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(54) Title: GLYCINAMIDE DERIVATIVES AS RAF-KINASE INHIBITORS

(57) Abstract: The present invention relates to glycinamide derivatives of formula (I), the use of the compounds of formula (I) as inhibitors of raf-kinase, the use of the compounds of formula (I) for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient.

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## GLYCINAMIDE DERIVATIVES AS RAF-KINASE INHIBITORS

5 The present invention relates to glycine amide derivatives, glycine amide derivatives as medicaments, glycine amide derivatives as inhibitors of raf-kinase, the use of glycine amide derivatives for the manufacture of a pharmaceutical, a method for producing a pharmaceutical composition containing said glycine amide derivatives, the pharmaceutical composition obtainable by said method and a method of treatment, comprising administering said pharmaceutical composition.

10 Protein phosphorylation is a fundamental process for the regulation of cellular functions. The coordinated action of both protein kinases and phosphatases controls the levels of phosphorylation and, hence, the activity of specific target proteins. One of the predominant roles of protein phosphorylation is in signal transduction, where extracellular signals are amplified and propagated by a cascade of protein phosphorylation and dephosphorylation events, e.g. in the p21<sup>ras</sup>/raf pathway.

20 The p21<sup>ras</sup> gene was discovered as an oncogene of the Harvey (rasH) and Kirsten (rasK) rat sarcoma viruses. In humans, characteristic mutations in the cellular ras gene (c-ras) have been associated with many different types of cancers. These mutant alleles, which render Ras constitutively active, have been shown to transform cells, such as the murine cell line NIH 3T3, in culture.

25 The p21<sup>ras</sup> oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30 % of all human cancers (Bolton et al. (1994) Ann. Rep. Med. Chem., 29, 165-74; Bos. (1989) Cancer Res., 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction cascade directed by growth factor receptors in almost all tissues (Avruch et al. (1994) Trends Biochem. Sci., 19, 279-83).

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Biochemically, ras is a guanine nucleotide binding protein, and cycling between a GTP-bound activated and a GDP-bound resting form is strictly controlled by ras endogenous GTPase activity and other regulatory proteins. The ras gene product binds to guanine triphosphate (GTP) and guanine diphosphate (GDP) and hydrolyzes GTP to GDP. It is the GTP-bound state of Ras that is active. In the ras mutants in cancer cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the cancerous growth of the cells which carry these mutants (Magnuson et al. (1994) *Semin. Cancer Biol.*, 5, 247-53). The ras proto-oncogene requires a functionally intact c-raf1 proto-oncogene in order to transduce growth and differentiation signals initiated by receptor and non-receptor tyrosine kinases in higher eukaryotes.

Activated Ras is necessary for the activation of the c-raf1 proto-oncogene, but the biochemical steps through which Ras activates the Raf-1 protein (Ser/Thr) kinase are now well characterized. It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase or dominant negative MEK (MAPKK), the substrate of raf kinase, leads to the reversion of transformed cells to the normal growth phenotype see: Daum et al. (1994) *Trends Biochem. Sci.*, 19, 474-80; Fridman et al. (1994) *J Biol. Chem.*, 269, 30105-8. Kolch et al. (1991) *Nature*, 349, 426-28) and for review Weinstein-Oppenheim et al. *Pharm. & Therap.* (2000), 88, 229-279.

Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types (Monia et al., *Nat. Med.* 1996, 2, 668-75).

Raf serine- and threonine-specific protein kinases are cytosolic enzymes that stimulate cell growth in a variety of cell systems (Rapp, U.R., et al.

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(1988) in The oncogene handbook; T. Curran, E.P. Reddy, and A. Skalka (ed.) Elsevier Science Publishers; The Netherlands, pp. 213-253; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184; Rapp, U.R., et al. (1990) Inv Curr. Top. Microbiol. Amunol. Potter and Melchers (eds), Berlin, Springer-Verlag 166:129-139).

Three isozymes have been characterized:

c-Raf (Raf-1) (Bonner, T.I., et al. (1986) Nucleic Acids Res. 14:1009-1015). A-Raf (Beck, T.W., et al. (1987) Nucleic Acids Res. 15:595-609), and B-Raf (Qkawa, S., et al. (1998) Mol. Cell. Biol. 8:2651-2654; Sithanandam, G. et a. (1990) Oncogene:1775). These enzymes differ in their expression in various tissues. Raf-1 is expressed in all organs and in all cell lines that have been examined, and A- and B-Raf are expressed in urogenital and brain tissues, respectively (Storm, S.M. (1990) Oncogene 5:345-351).

Raf genes are proto-oncogenes: they can initiate malignant transformation of cells when expressed in specifically altered forms. Genetic changes that lead to oncogenic activation generate a constitutively active protein kinase by removal or interference with an N-terminal negative regulatory domain of the protein (Heidecker, G., et al. (1990) Mol. Cell. Biol. 10:2503-2512; Rapp, U.R., et al. (1987) in Oncogenes and cancer S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed). Japan Scientific Press, Tokyo). Microinjection into NIH 3T3 cells of oncogenically activated but not wild-type versions of the Raf-protein prepared with Escherichia coli expression vectors results in morphological transformation and stimulates DNA synthesis (Rapp, U.R., et al. (1987) in Oncogenes and cancer; S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed.) Japan Scientific Press, Tokyo; Smith, M. R., et al (1990) Mol. Cell. Biol. 10:3828-3833). Activating mutants of B-Raf have been identified in a wide range of human cancers



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e.g. colon, ovarien, melanomas and sarcomas (Davies, H., et al. (2002), Nature 417 949-945. Published online June 9, 2002, 10.1038/nature00766). The preponderant mutation is a single phosphomimetic substitution in the kinase activation domain (V599E),  
5 leading to constitutive kinase activity and transformation of NIH3T3 cells.

Thus, activated Raf-1 is an intracellular activator of cell growth. Raf-1 protein serine kinase in a candidate downstream effector of mitogen signal transduction, since Raf oncogenes overcome growth arrest resulting from  
10 a block of cellular ras activity due either to a cellular mutation (ras revertant cells) or microinjection of anti-ras antibodies (Rapp, U.R., et al. (1988) in The Oncogene Handbook, T. Curran, E.P. Reddy, and A. Skalka (ed.), Elsevier Science Publishers; The Netherlands, pp. 213-253; Smith, M.R., et al. (1986) Nature (London) 320:540-543).

15 c-Raf function is required for transformation by a variety of membrane-bound oncogenes and for growth stimulation by mitogens contained in serums (Smith, M.R., et al. (1986) Nature (London) 320:540-543). Raf-1 protein serine kinase activity is regulated by mitogens via phosphorylation  
20 (Morrison, D.K., et al. (1989) Cell 58:648-657), which also effects sub cellular distribution (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184. Raf-1 activating growth factors include platelet-derived growth factor (PDGF) (Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859),  
25 colony-stimulating factor (Baccarini, M., et al. (1990) EMBO J. 9:3649-3657), insulin (Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12115-12118), epidermal growth factor (EGF) (Morrison, R.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), interleukin 2 (Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227), and interleukin 3 and  
30 granulocytemacrophage colony-stimulating factor (Carroll, M.P., et al (1990) J. Biol. Chem. 265:19812-19817).

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Upon mitogen treatment of cells, the transiently activated Raf-1 protein serine kinase translocates to the perinuclear area and the nucleus (Olah, Z., et al. (1991) *Exp. Brain Res.* 84:403; Rapp, U.R., et al. (1988) *Cold Spring Harbor Sym. Quant. Biol.* 53:173-184). Cells containing activated Raf are altered in their pattern of gene expression (Heidecker, G., et al. (1989) in *Genes and signal transduction in multistage carcinogenesis*, N. Colburn (ed.), Marcel Dekker, Inc., New York, pp. 339-374), and Raf oncogenes activate transcription from Ap-1/PEA3-dependent promoters in transient transfection assays (Jamal, S., et al (1990) *Science* 344:463-466; Kaibuchi, K., et al (1989) *J. Biol. Chem.* 264:20855-20858; Wasylyk, C., et al. (1989) *Mol. Cell. Biol.* 9:2247-2250).

There are at least two independent pathways for Raf-1 activation by extracellular mitogens: one involving protein kinase C (KC) and a second initiated by protein tyrosine kinases (Blackshear, P.J., et al. (1990) *J. Biol. Chem.* 265:12131-12134; Kovacina, K.S., et al (1990) *J. Biol. Chem.* 265:12115-12118; Morrison, D.K., et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:8855-8859; Siegel, J.N., et al (1990) *J. Biol. Chem.* 265:18472-18480; Turner, B.C., et al (1991) *Proc. Natl. Acad. Sci. USA* 88:1227). In either case, activation involves Raf-1 protein phosphorylation. Raf-1 phosphorylation may be a consequence of a kinase cascade amplified by autophosphorylation or may be caused entirely by autophosphorylation initiated by binding of a putative activating ligand to the Raf-1 regulatory domain, analogous to PKC activation by diacylglycerol (Nishizuka, Y. (1986) *Science* 233:305-312).

The process of angiogenesis is the development of new blood vessels, generally capillaries, from pre-existing vasculature. Angiogenesis is defined as involving (i) activation of endothelial cells; (ii) increased vascular permeability; (iii) subsequent dissolution of the basement membrane and extravasation of plasma components leading to formation of a provisional fibrin gel extracellular matrix; (iv) proliferation and

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mobilization of endothelial cells; (v) reorganization of mobilized endothelial cells to form functional capillaries; (vi) capillary loop formation; and (vii) deposition of basement membrane and recruitment of perivascular cells to newly formed vessels.

5

Normal angiogenesis is activated during tissue growth, from embryonic development through maturity, and then enters a period of relative quiescence during adulthood.

10

Normal angiogenesis is also activated during wound healing, and at certain stages of the female reproductive cycle. Inappropriate or pathological angiogenesis has been associated with several disease states including various retinopathies; ischemic disease; atherosclerosis; chronic inflammatory disorders; rheumatoid arthritis, and cancer. The role of angiogenesis in disease states is discussed, for instance, in Fan et al, Trends in Pharmacol Sci. 16:54-66; Shawver et al, DOT Vol. 2, No. 2 February 1997; Folkman, 1995, Nature Medicine 1:27-31.

15

In cancer the growth of solid tumors has been shown to be angiogenesis dependent. (See Folkman, J., J. Nat'l. Cancer Inst., 1990, 82, 4-6.) Consequently, the targeting of pro-angiogenic pathways is a strategy being widely pursued in order to provide new therapeutics in these areas of great, unmet medical need.

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25

Raf is involved in angiogenic processes. Endothelial growth factors (e.g. vascular endothelial growth factor VEGF) activates receptor tyrosine kinases (e.g. VEGFR-2) and signal through the Ras/Raf/Mek/Erk kinase cascade. Activation of VEGFR-2 by VEGF is a critical step in the signal transduction pathway that initiates tumor angiogenesis. VEGF expression may be constitutive to tumor cells and can also be upregulated in response to certain stimuli. One such stimuli is hypoxia, where VEGF expression is

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upregulated in both tumor and associated host tissues. The VEGF ligand activates VEGFR-2 by binding with its extracellular VEGF binding site. This leads to receptor dimerization of VEGFRs and autophosphorylation of tyrosine residues at the intracellular kinase domain of VEGFR- 2. The  
5 kinase domain operates to transfer a phosphate from ATP to the tyrosine residues, thus providing binding sites for signaling proteins downstream of VEGFR-2 leading ultimately to initiation of angiogenesis (McMahon, G., The Oncologist, Vol. 5, No. 90001, 3-10, April 2000).

10 Mice with a targeted disruption in the Braf gene die of vascular defects during development (Wojnowski, L. et al. 1997, Nature genetics 16, page 293- 296). These mice show defects in the formation of the vascular system and in angiogenesis e.g. enlarged blood vessels and increased apoptotic death of differentiated endothelial cells.

15 For the identification of a signal transduction pathway and the detection of cross talks with other signaling pathways suitable models or model systems have been generated by various scientists, for example cell culture models (e.g. Khwaja et al., EMBO, 1997, 16, 2783-93) and  
20 transgenic animal models (e.g. White et al., Oncogene, 2001, 20, 7064-7072). For the examination of particular steps in the signal transduction cascade, interfering compounds can be used for signal modulation (e.g. Stephens et al., Biochemical J., 2000, 351, 95-105). The compounds according to the invention may also be useful as reagents for the  
25 examination of kinase dependent signal transduction pathways in animal and/or cell culture models or any of the clinical disorders listed throughout this application.

30 The measurement of kinase activity is a well known technique feasible for each person skilled in the art. Generic test systems for kinase activity detection with substrates, for example histone (e.g. Alessi et al., FEBS Lett. 1996, 399, 3, page 333-8) or myelin basic protein are well described

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in the literature (e.g. Campos-González, R. and Glenney, Jr., J.R. 1992 *J. Biol. Chem.* 267, Page 14535).

5 For the identification of kinase inhibitors various assay systems are available (see for example Walters et al., *Nature Drug Discovery* 2003, 2; page 259-266). For example, in scintillation proximity assays (e.g. Sorg et al., *J. of. Biomolecular Screening*, 2002, 7, 11-19) or flashplate assays the radioactive phosphorylation of a protein or peptide as substrate with  $\gamma$ ATP can be measured. In the presence of an inhibitory compound no signal or  
10 a decreased radioactive signal is detectable. Furthermore homogeneous time-resolved fluorescence resonance energy transfer (HTR-FRET), and fluorescence polarization (FP) technologies are useful for assay methods (for example Sills et al., *J. of Biomolecular Screening*, 2002, 191-214).

15 Other non-radioactive ELISA based assay methods use specific phospho-antibodies (AB). The phospho-AB binds only the phosphorylated substrate. This binding is detectable with a secondary peroxidase conjugated antibody, measured for example by chemiluminescence (for exaple Ross et al., *Biochem. J.*, 2002, 366, 977-981).  
20

The present invention provides compounds generally described as glycine amide derivatives, including both aryl and/or heteroaryl derivatives, which are preferably inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of p21<sup>ras</sup>, the inhibitors are useful in pharmaceutical  
25 compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid cancers, e.g. murine cancer, since the progression of these cancers is dependent upon the ras protein signal  
30 transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the

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compound of Formula I or a pharmaceutically acceptable salt thereof is administered for the treatment of diseases mediated by the raf kinase pathway especially cancers, including solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma), pathological angiogenesis and metastatic cell migration. Furthermore the compounds are useful in the treatment of complement activation dependent chronic inflammation (Niculescu et al. (2002) Immunol. Res., 24:191-199) and HIV-1 (human immunodeficiency virus type1) induced immunodeficiency (Popik et al. (1998) J Virol, 72: 6406-6413).

Therefore, subject of the present invention are glycinamide derivatives of formula I

A-D-B

(I)

wherein

D is a bivalent glycinamide moiety which is bonded to A and B, preferably to one bonding partner via the N-nitrogen atom and to the other bonding partner via the N'-nitrogen atom, wherein the N-nitrogen atom and/or the N'-nitrogen atom is unsubstituted or substituted with one or more substituents, wherein said substituents are preferably selected from the group consisting of alkyl, alkylene, haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkylene, heterocyclyl, aryl, aralkyl, heteroaryl, hydroxy, alkoxy, haloalkoxy, aralkoxy, aryloxy, mercapto, alkylsulfanyl, haloalkylsulfanyl, arylsulfanyl, heteroaryl-sulfanyl, alkylsulfenyl, haloalkylsulfenyl, arylsulfenyl, heteroaryl-sulfenyl, alkylsulfonyl, haloalkylsulfonyl, arylsulfonyl, heteroaryl-sulfonyl, carboxy, cyano, cyanoalkyl, aminosulfonyl, acyl, acyloxy, carbamoyl, aroyl, heteroaryl, heteroaroyloxy, unsubstituted

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amino groups and substituted amino groups, and wherein the carbonyl group of said glycine amide moiety can be derivatized, preferably to a C=S, C=NR<sup>5</sup>, C=C(R<sup>5</sup>)-NO<sub>2</sub>, C=C(R<sup>5</sup>)-CN or C=C(CN)<sub>2</sub> group,

5

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L')<sub>α</sub>, where L is a 5, 6 or 7 membered cyclic structure, preferably selected from the group consisting of aryl, heteroaryl, arylene and heteroarylene, bound directly to D, L' comprises an optionally substituted cyclic moiety having at least 5 members, preferably selected from the group consisting of aryl, heteroaryl, aralkyl, cycloalkyl and heterocyclyl, M is a bond or a bridging group having at least one atom, α is an integer of from 1-4; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein L' is preferably substituted by at least one substituent which is preferably selected from the group consisting of -SO<sub>β</sub>R<sub>x</sub>, -C(O)R<sub>x</sub> and -C(NR<sub>y</sub>)R<sub>z</sub>,

10

15

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms, preferably of up to 20 carbon atoms, comprising at least one 5-, 6-, or 7-membered cyclic structure, preferably a 5- or 6-membered cyclic structure, bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein said cyclic structure directly bound to D is preferably selected from the group consisting of aryl, heteroaryl and heterocyclyl,

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R<sub>y</sub> is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

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$R_z$  is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

$R_x$  is  $R_z$  or  $NR_aR_b$ , where  $R_a$  and  $R_b$  are

a) independently hydrogen, a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms, selected from N, S and O, and are optionally substituted by halogen, or

$-OSi(R_f)_3$  where  $R_f$  is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, and are optionally substituted by halogen; or

b)  $R_a$  and  $R_b$  together from a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or one of  $R_a$  or  $R_b$  is  $-C(O)-$ , a  $C_1-C_5$  divalent alkylene group or a substituted  $C_1-C_5$  divalent alkylene group bound to the moiety L



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to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C<sub>1</sub>-C<sub>5</sub> divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; where B is substituted, L is substituted or L' is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo and W<sub>γ</sub>, where γ is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO<sub>2</sub>R, -C(O)NR<sup>5</sup>R<sup>5</sup>, -C(O)-R<sup>5</sup>, -NO<sub>2</sub>, -OR<sup>5</sup>, -SR<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>H, -NR<sup>5</sup>R<sup>5</sup>, -NR<sup>5</sup>C(O)OR<sup>5</sup>, -NR<sup>5</sup>C(O)R<sup>5</sup>, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of -CN, -CO<sub>2</sub>R, -C(O)NR<sup>5</sup>R<sup>5</sup>, -C(O)-R<sup>5</sup>, -NO<sub>2</sub>, -OR<sup>5</sup>, -SR<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>H, -NR<sup>5</sup>R<sup>5</sup>, -NR<sup>5</sup>C(O)OR<sup>5</sup>, -NR<sup>5</sup>C(O)R<sup>5</sup> and halogen up to per-halo; with each R<sup>5</sup> independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen;

wherein Q is -O-, -S-, -N(R<sup>5</sup>)-, -(CH<sub>2</sub>)<sub>β</sub>-, -C(O)-, -CH(OH)-, -(CH<sub>2</sub>)<sub>β</sub>-O-, -(CH<sub>2</sub>)<sub>β</sub>-S-, -(CH<sub>2</sub>)<sub>β</sub>N(R<sup>5</sup>)-, -O(CH<sub>2</sub>)<sub>β</sub>-CHHal-, -CHal<sub>2</sub>-, -S-(CH<sub>2</sub>)- and -N(R<sup>5</sup>)(CH<sub>2</sub>)<sub>β</sub>- where β = 1-3, and Hal is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z<sub>δ1</sub> wherein δ1 is 0 to 3 and

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each Z is independently selected from the group consisting -CN, -CO<sub>2</sub>R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>5</sup>, -C(O)-R<sup>5</sup>, -NO<sub>2</sub>, -OR<sup>5</sup>, -SR<sup>5</sup>, -NR<sup>5</sup>R<sup>5</sup>, -NR<sup>5</sup>C(O)OR<sup>5</sup>, -NR<sup>5</sup>C(O)R<sup>5</sup>, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>5</sup>, -C(O)-R<sup>5</sup>, -NO<sub>2</sub>, -OR<sup>5</sup>, -SR<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>H, -NR<sup>5</sup>R<sup>5</sup>, -NR<sup>5</sup>C(O)OR<sup>5</sup>, -NR<sup>5</sup>C(O)R<sup>5</sup>, and with R<sup>5</sup> as defined above.

More preferred, in the compound of formula I,

R<sub>y</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, C<sub>2-10</sub> alkenyl, C<sub>1-10</sub> alkenoyl, C<sub>6-12</sub> aryl, C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from N, S and O, C<sub>7-24</sub> aralkyl, C<sub>7-24</sub> alkaryl, substituted C<sub>1-10</sub> alkyl, substituted C<sub>1-10</sub> alkoxy, substituted C<sub>3-10</sub> cycloalkyl having 0-3 heteroatoms selected from N, S and O, substituted C<sub>6-C14</sub> aryl, substituted C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C<sub>7-24</sub> alkaryl or substituted C<sub>7-24</sub> aralkyl, where R<sub>y</sub> is a substituted group, it is substituted by halogen up to per halo,

R<sub>z</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, C<sub>3-10</sub> cycloalkyl having 0-3 heteroatoms, C<sub>2-10</sub> alkenyl, C<sub>1-10</sub> alkenoyl, C<sub>6-12</sub> aryl, C<sub>3-C12</sub> hetaryl having 1-3 heteroatoms selected from S, N and O, C<sub>7-24</sub> alkaryl, C<sub>7-24</sub> aralkyl, substituted C<sub>3-C10</sub> cycloalkyl having 0-3 heteroatoms selected from S, N and O, substituted C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from S, N and O, substituted C<sub>7-24</sub> alkaryl or substituted C<sub>7-C24</sub> aralkyl where R<sub>z</sub> is a substituted group, it is substituted by halogen up to per halo, hydroxy, C<sub>1-10</sub> alkyl, C<sub>3-12</sub> cycloalkyl having 0-3 heteroatoms selected from N, S and O, substituted C<sub>3-C12</sub> hetaryl having 1-3 heteroatoms selected from N, S and O, C<sub>1-10</sub> alkoxy, C<sub>6-12</sub> aryl, C<sub>1-6</sub> halo substituted alkyl up to per halo alkyl, C<sub>6-C12</sub> halo

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substituted aryl up to per halo aryl, C<sub>3</sub>-C<sub>12</sub> halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C<sub>3</sub>-C<sub>12</sub> hetaryl up to per halo, hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted C<sub>7</sub>-C<sub>24</sub> aralkyl up to per halo aralkyl, halo substituted C<sub>7</sub>-C<sub>24</sub> alkaryl up to per halo alkaryl, and -C(O)R<sub>g</sub>,

R<sub>a</sub> and R<sub>b</sub> are:

- a) independently hydrogen, a carbon based moiety selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, C<sub>3-10</sub> cycloalkyl, C<sub>2-10</sub> alkenyl, C<sub>1-10</sub> alkenoyl, C<sub>6-12</sub> aryl, C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from O, N and S, C<sub>3-12</sub> cycloalkyl having 0-3 heteroatoms selected from N, S and O, C<sub>7-24</sub> aralkyl, C<sub>7</sub>-C<sub>24</sub> alkaryl, substituted C<sub>1-10</sub> alkyl, substituted C<sub>1-10</sub> alkoxy, substituted C<sub>3-10</sub> cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C<sub>6-12</sub> aryl, substituted C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C<sub>7-24</sub> aralkyl, substituted C<sub>7-24</sub> alkaryl; where R<sub>a</sub> and R<sub>b</sub> are a substituted group, they are substituted by halogen up to per halo, hydroxy, C<sub>1-10</sub> alkyl, C<sub>3-12</sub> cycloalkyl having 0-3 heteroatoms selected from O, S and N, C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from N, S and O, C<sub>1-10</sub> alkoxy, C<sub>6-12</sub> aryl, C<sub>1-6</sub> halo substituted alkyl up to per halo alkyl, C<sub>6</sub>-C<sub>12</sub> halo substituted aryl up to per halo aryl, C<sub>3</sub>-C<sub>12</sub> halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C<sub>3</sub>-C<sub>12</sub> hetaryl up to per halo heteraryl, halo substituted C<sub>7</sub>-C<sub>24</sub> aralkyl up to per halo aralkyl, halo substituted C<sub>7</sub>-C<sub>24</sub> alkaryl up to per halo alkaryl, and -C(O)R<sub>g</sub>; or
- OSi(R<sub>f</sub>)<sub>3</sub> where R<sub>f</sub> is hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy, C<sub>3-10</sub> cycloalkyl, C<sub>2-10</sub> alkenyl, C<sub>1-10</sub> alkenoyl, C<sub>6-12</sub> aryl, C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from O, N and S, C<sub>3-12</sub>

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- 5 cycloalkyl having 0-3 heteroatoms selected from N, S and O, C<sub>7-24</sub> aralkyl, C<sub>7-24</sub> alkaryl, substituted C<sub>1-10</sub> alkyl, substituted C<sub>1-10</sub> alkoxy, substituted C<sub>3-10</sub> cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C<sub>6-12</sub> aryl, substituted C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C<sub>7-24</sub> aralkyl, substituted C<sub>7-24</sub> alkaryl, or
- 10 b) R<sub>a</sub> and R<sub>b</sub> together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O with substituents selected from the group consisting of halogen up to per halo, hydroxy, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, C<sub>3-10</sub> cycloalkyl, C<sub>2-10</sub> alkenyl, C<sub>1-10</sub> alkenoyl, C<sub>6-12</sub> aryl, C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from O, N and S, C<sub>3-12</sub> cycloalkyl having 0-3 heteroatoms selected from N, S and O, C<sub>7-24</sub> aralkyl, C<sub>7-24</sub> alkaryl, substituted C<sub>1-10</sub> alkyl, substituted C<sub>1-10</sub> alkoxy, substituted C<sub>3-10</sub> cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C<sub>6-12</sub> aryl, substituted C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C<sub>7-24</sub> aralkyl, substituted C<sub>7-24</sub> alkaryl, where R<sub>a</sub> and R<sub>b</sub> are a substituted group, they are substituted by halogen up to per halo, hydroxy, C<sub>1-10</sub> alkyl, C<sub>3-12</sub> cycloalkyl having 0-3 heteroatoms selected from O, S and N, C<sub>3-12</sub> hetaryl having 1-3 heteroatoms selected from N, S and O, C<sub>1-10</sub> alkoxy, C<sub>6-12</sub> aryl, C<sub>1-6</sub> halo substituted alkyl up to per halo alkyl, C<sub>6-12</sub> halo substituted aryl up to per halo aryl, C<sub>3-12</sub> halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C<sub>3-12</sub> hetaryl up to per halo heteraryl, halo substituted C<sub>7-24</sub> aralkyl up to per halo aralkyl, halo substituted C<sub>7-24</sub> alkaryl up to per halo alkaryl, and -C(O)R<sub>g</sub>,
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or

- 5 c) one of  $R_a$  or  $R_b$  is  $-C(O)-$ , a  $C_1-C_5$  divalent alkylene group or a substituted  $C_1-C_5$  divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted  $C_1-C_5$  divalent alkylene group are selected from the group consisting of halogen, hydroxy,  $C_{1-10}$  alkyl,  $C_{3-12}$  cycloalkyl having 0-3 heteroatoms selected from, S, O and N,  $C_{3-12}$  hetaryl having 1-3 heteroatoms selected from N, S and O,  $C_{1-10}$  alkoxy,  $C_{6-12}$  aryl,  $C_7-C_{24}$  alkaryl,  $C_7-C_{24}$  aralkyl,  $C_{1-6}$  halo substituted alkyl up to per halo alkyl,  $C_6-C_{12}$  halo substituted aryl up to per halo aryl,  $C_3-C_{12}$  halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted  $C_3-C_{12}$  hetaryl up to per halo heteraryl, halo substituted  $C_7-C_{24}$  aralkyl up to per halo aralkyl, halo substituted  $C_7-C_{24}$  alkaryl up to per halo alkaryl, and  $-C(O)R_g$ ,  
 10 where  $R_g$  is  $C_{1-10}$  alkyl;  $-CN$ ,  $-CO_2R_d$ ,  $-OR_d$ ,  $-SR_d$ ,  $-SO_2R_d$ ,  $-SO_3H$ ,  $-NO_2$ ,  $-C(O)R_e$ ,  $-NR_dR_e$ ,  $-NR_dC(O)OR_e$  and  $-NR_d(CO)R_e$  and  $R_d$  and  $R_e$  are independently selected from the group consisting of hydrogen,  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy,  $C_{3-10}$  cycloalkyl having 0-3 heteroatoms selected from O, N and S,  $C_{6-12}$  aryl,  $C_3-C_{12}$  hetaryl with 1-3 heteroatoms selected from O, N and S,  $C_7-C_{24}$  aralkyl,  $C_7-C_{24}$  alkaryl, up to per halo substituted  $C_1-C_{10}$  alkyl, up to per halo substituted  $C_3-C_{10}$  cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted  $C_6-C_{14}$  aryl, up to per halo substituted  $C_3-C_{12}$  hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted  $C_7-C_{24}$  alkaryl up to per halo alkaryl, and up to per halo substituted  $C_7-C_{24}$  aralkyl,
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W is independently selected from the group consisting  $-\text{CN}$ ,  $-\text{CO}_2\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^5$ ,  $-\text{C}(\text{O})-\text{R}^5$ ,  $-\text{NO}_2$ ,  $-\text{OR}^5$ ,  $-\text{SR}^5$ ,  $-\text{SO}_2\text{R}^5$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{NR}^5\text{R}^5$ ,  $-\text{NR}^5\text{C}(\text{O})\text{OR}^5$ ,  $-\text{NR}^5\text{C}(\text{O})\text{R}^5$ ,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_1\text{-C}_{10}$  alkoxy,  $\text{C}_2\text{-C}_{10}$  alkenyl,  $\text{C}_1\text{-C}_{10}$  alkenoyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl having 0-3 heteroatoms selected from O, S and N,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_7\text{-C}_{24}$  alkaryl,  $\text{C}_7\text{-C}_{24}$  aralkyl,  $\text{C}_3\text{-C}_{12}$  heteroaryl having 1-3 heteroatoms selected from O, N and S,  $\text{C}_4\text{-C}_{23}$  alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted  $\text{C}_1\text{-C}_{10}$  alkyl, substituted  $\text{C}_1\text{-C}_{10}$  alkoxy, substituted  $\text{C}_2\text{-C}_{10}$  alkenyl, substituted  $\text{C}_1\text{-C}_{10}$  alkenoyl, substituted  $\text{C}_3\text{-C}_{10}$  cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted  $\text{C}_6\text{-C}_{12}$  aryl, substituted  $\text{C}_3\text{-C}_{12}$  hetaryl having 1-3 heteroatoms selected from O, N and S, substituted  $\text{C}_7\text{-C}_{24}$  aralkyl, substituted  $\text{C}_7\text{-C}_{24}$  alkaryl, substituted  $\text{C}_4\text{-C}_{23}$  alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and  $-\text{Q-Ar}$ ;

$\text{R}^5$  is independently selected from H,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_1\text{-C}_{10}$  alkoxy,  $\text{C}_2\text{-C}_{10}$  alkenyl,  $\text{C}_1\text{-C}_{10}$  alkenoyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl having 0-3 heteroatoms selected from O, S and N,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_3\text{-C}_{13}$  hetaryl having 1-3 heteroatoms selected from O, N and S,  $\text{C}_7\text{-C}_{14}$  alkaryl,  $\text{C}_7\text{-C}_{24}$  aralkyl,  $\text{C}_4\text{-C}_{23}$  alkheteroaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted  $\text{C}_1\text{-C}_{10}$  alkyl, up to per-halosubstituted  $\text{C}_3\text{-C}_{10}$  cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per-halosubstituted  $\text{C}_6\text{-C}_{14}$  aryl, up to per-halosubstituted  $\text{C}_3\text{-C}_{13}$  hetaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted  $\text{C}_7\text{-C}_{24}$  aralkyl, up to per-halosubstituted  $\text{C}_7\text{-C}_{24}$  alkaryl, and up to per-halosubstituted  $\text{C}_4\text{-C}_{23}$  alkheteroaryl; and each

Z is independently selected from the group consisting  $-\text{CN}$ ,  $-\text{CO}_2\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^5$ ,  $-\text{C}(\text{O})-\text{R}^5$ ,  $-\text{NO}_2$ ,  $-\text{OR}^5$ ,  $-\text{SR}^5$ ,  $-\text{SO}_2\text{R}^5$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{NR}^5\text{R}^5$ ,  $-\text{NR}^5\text{C}(\text{O})\text{OR}^5$ ,  $-\text{NR}^5\text{C}(\text{O})\text{R}^5$ ,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_1\text{-C}_{10}$  alkoxy,  $\text{C}_2\text{-C}_{10}$  alkenyl,  $\text{C}_1\text{-C}_{10}$  alkenoyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl having 0-3 heteroatoms selected from O, S and N,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_7\text{-C}_{24}$  alkaryl,  $\text{C}_7\text{-C}_{24}$  aralkyl,

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C<sub>3</sub>-C<sub>12</sub> heteroaryl having 1-3 heteroatoms selected from O, N and S,  
 C<sub>4</sub>-C<sub>23</sub> alkheteroaryl having 1-3 heteroatoms selected from O, N and  
 S, substituted C<sub>1</sub>-C<sub>10</sub> alkyl, substituted C<sub>1</sub>-C<sub>10</sub> alkoxy, substituted  
 C<sub>2</sub>-C<sub>10</sub> alkenyl, substituted C<sub>1</sub>-C<sub>10</sub> alkenoyl, substituted C<sub>3</sub>-C<sub>10</sub>  
 5 cycloalkyl having 0-3 heteroatoms selected from O, N and S,  
 substituted C<sub>6</sub>-C<sub>12</sub> aryl, substituted C<sub>3</sub>-C<sub>12</sub> hetaryl having 1-3  
 heteroatoms selected from O, N and S; wherein if Z is a substituted  
 group, the one or more substituents are selected from the group  
 consisting of -CN, -CO<sub>2</sub>R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>5</sup>, -C(O)-R<sup>5</sup>, -NO<sub>2</sub>, -OR<sup>5</sup>, -SR<sup>5</sup>,  
 10 -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>H, -NR<sup>5</sup>R<sup>5</sup>, -NR<sup>5</sup>C(O)OR<sup>5</sup>, -NR<sup>5</sup>C(O)R<sup>5</sup>.

According to the invention, each M independently from one another  
 represents a bond OR is a bridging group, selected from the group  
 consisting of (CR<sup>5</sup>R<sup>5</sup>)<sub>h</sub>, or (CHR<sup>5</sup>)<sub>h</sub>-Q-(CHR<sup>5</sup>)<sub>i</sub>, wherein

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Q is selected from a group consisting of O, S, N-R<sup>5</sup>, (CHAl<sub>2</sub>)<sub>j</sub>, (O-CHR<sup>5</sup>)<sub>j</sub>,  
 (CHR<sup>5</sup>-O)<sub>j</sub>, CR<sup>5</sup>=CR<sup>5</sup>, (O-CHR<sup>5</sup>CHR<sup>5</sup>)<sub>j</sub>, (CHR<sup>5</sup>CHR<sup>5</sup>-O)<sub>j</sub>, C=O, C=S,  
 C=NR<sup>5</sup>, CH(OR<sup>5</sup>), C(OR<sup>5</sup>)(OR<sup>5</sup>), C(=O)O, OC(=O), OC(=O)O,  
 C(=O)N(R<sup>5</sup>), N(R<sup>5</sup>)C(=O), OC(=O)N(R<sup>5</sup>), N(R<sup>5</sup>)C(=O)O, CH=N-O,  
 20 CH=N-NR<sup>5</sup>, OC(O)NR<sup>5</sup>, NR<sup>5</sup>C(O)O, S=O, SO<sub>2</sub>, SO<sub>2</sub>NR<sup>5</sup> and NR<sup>5</sup>SO<sub>2</sub>,  
 wherein

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R<sup>5</sup> is in each case independently selected from the meanings given  
 above, preferably from hydrogen, halogen, alkyl, aryl, aralkyl,

h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6, preferably 0,  
 1, 2, or 3, and

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j is 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3.

More preferred, each M independently from one another represents a  
 bond or is a bridging group, selected from the group consisting of -O-, -S-,

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-N(R<sup>5</sup>)-, -(CH<sub>2</sub>)<sub>β</sub>-, -C(O)-, -CH(OH)-, -(CH<sub>2</sub>)<sub>β</sub>O-, -(CH<sub>2</sub>)<sub>β</sub>S-, -(CH<sub>2</sub>)<sub>β</sub>N(R<sup>5</sup>)-, -O(CH<sub>2</sub>)<sub>β</sub>-, -CHHal-, -CHal<sub>2</sub>-, -S-(CH<sub>2</sub>)<sub>β</sub>- and -N(R<sup>5</sup>)(CH<sub>2</sub>)<sub>β</sub>, where β is 1 to 6 and especially preferred 1 to 3, Hal is halogen and R<sup>5</sup> is as defined above. More preferred, the group B of Formula I is a substituted or unsubstituted  
5 six member aryl moiety or six member hetaryl moiety, said hetaryl moiety having 1 to 4 members selected from the group of hetaryl atoms consisting of nitrogen, oxygen and sulfur with the balance of the hetaryl moiety being carbon.

10 Even more preferred, the group B of Formula I is

- a) an unsubstituted phenyl group, an unsubstituted pyridyl group, an unsubstituted pyrimidinyl, a phenyl group substituted by a substituent selected from the group consisting of halogen and W<sub>γ</sub> wherein W and  
15 γ are as defined in claim 1, a pyrimidinyl group substituted by a substituent selected from the group constituting of halogen and W<sub>γ</sub>, whereas W and γ are as defined above, or a substituted pyridyl group, substituted by a substituent selected from the group consisting of halogen and W<sub>γ</sub> wherein W and γ are as defined above; or a  
20 substituted phenyl group, a substituted pyrimidinyl group, or substituted pyridyl group substituted 1 to 3 times by 1 or more substituents selected from the group consisting of -CN, halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkyl alkoxy, -OH, up to per halo substituted C<sub>1</sub>-C<sub>10</sub> alkyl, up to per halo substituted C<sub>1</sub>-C<sub>10</sub> alkoxy or phenyl  
25 substituted by halogen up to per halo; or
- b) a substituted phenyl group, a substituted pyrimidinyl group, or substituted pyridyl group substituted 1 to 3 times by 1 or more substituents selected from the group consisting of CN, halogen, alkyl,  
30 especially C<sub>1</sub>-C<sub>4</sub> alkyl, alkoxy, especially C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, up to per halo substituted alkyl, especially up to per halo substituted C<sub>1</sub>-C<sub>4</sub>



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alkyl, up to per halo substituted alkoxy, especially up to per halo substituted C<sub>1</sub>-C<sub>4</sub> alkoxy or phenyl substituted by halogen up to per halo.

5 In the formula I, the group L which is directly bound to D is preferably a substituted or unsubstituted 6 member aryl moiety or a substituted or unsubstituted 6 member hetaryl moiety, wherein said hetaryl moiety has 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulfur with the balance of said hetaryl moiety being  
10 carbon, wherein the one or more substituents are selected from the group consisting of halogen and W $\gamma$  wherein W and  $\gamma$  are as defined above.

More preferred, the group L is a substituted phenyl, unsubstituted phenyl, substituted pyrimidinyl, unsubstituted pyrimidinyl, substituted pyridyl or  
15 unsubstituted pyridyl group.

In the formula I, the group L' preferably comprises a 5 to 6 membered aryl moiety or hetaryl moiety, wherein said heteraryl moiety comprises 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulfur.  
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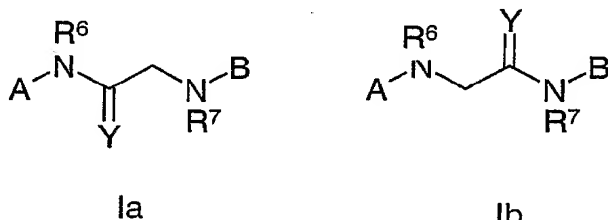
More preferred, the group L' is phenyl, pyridinyl or pyrimidinyl.

According to the invention, a bivalent glycinamide moiety is preferably a  
25 bivalent radical derived from substituted or unsubstituted, preferably unsubstituted amide of the amino acid glycine, or a derivative thereof. If the amide of the amino acid glycine is substituted, it is preferably mono substituted on the nitrogen atom of the amide group and/or mono substituted on the nitrogen atom of the amino group. Preferably, the  
30 substituted or unsubstituted amide of the amino acid glycine is bonded to A and B via its nitrogen atoms of the amide group and the amino group,

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respectively. This kind of linkage is usually referred to as an N,N'-linkage. The hydrogen atoms of one or both nitrogen atoms of the glycine amide moiety can be substituted by suitable substituents, preferably selected from the group consisting of alkyl, alkylene, haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkylene, heterocyclyl, aryl, aralkyl, heteroaryl, carboxy, cyanoalkyl, acyl and heteroaryl. Preferably, both nitrogen atoms of the glycine amide moiety are unsubstituted. Therefore, D is more preferred an unsubstituted amide of the amino acid glycine, which is bonded to the radicals A and B via its N,N'-atoms, or a derivative thereof. In this respect, one or both of the nitrogen atoms of D can, independently from one another, optionally be deprotonated, protonated and/or quarternized. The resulting ions or salts are also subject of the present invention. Derivatives of the glycine amide moiety according to the invention are preferably derivatives, wherein the carbonyl group of said glycine amide moiety is derivatized to a C=S, C=NR<sup>5</sup>, C=C(R<sup>5</sup>)-NO<sub>2</sub>, C=C(R<sup>5</sup>)-CN or C=C(CN)<sub>2</sub> group.

Accordingly, preferred compounds of formula I are of formula Ia and/or Ib

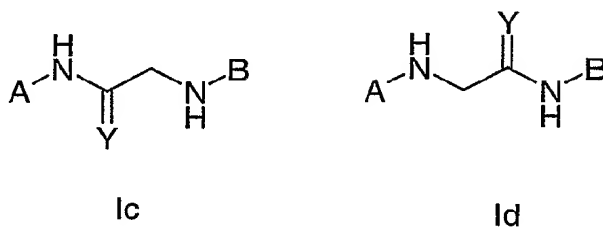


wherein A and B are as defined above/below, Y is selected from O, S, NR<sup>5</sup>, C(R<sup>5</sup>)-NO<sub>2</sub>, C(R<sup>5</sup>)-CN and C=C(CN)<sub>2</sub>, and wherein R<sup>6</sup> and R<sup>7</sup> are independently selected from the group consisting of H, alkyl, alkylene, haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkylene, heterocyclyl, aryl, aralkyl, heteroaryl, carboxy, cyanoalkyl, acyl and heteroaryl, and the salts or solvates thereof. More preferred are compounds of formula Ia and/or Ib,

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wherein Y is O and/or wherein one or both of the residues R<sup>6</sup> and R<sup>7</sup> are H, and the salts or solvates thereof.

Accordingly, one aspect of the instant invention relates to compounds of formula Ic and/or Id,



wherein A and B are as defined above/below, and the salts or solvates thereof.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, the term "alkyl" preferably refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylsulfanyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfenyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally

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substituted by alkyl, nitro, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

5

As used herein, the term "C<sub>1</sub>-C<sub>6</sub> alkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms.

Examples of branched or straight chained "C<sub>1</sub>-C<sub>6</sub> alkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, t-butyl, n-pentyl and isopentyl.

10

As used herein, the term "alkylene" preferably refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl, optionally substituted by alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed.

15

Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene and the like.

20

As used herein, the term "C<sub>1</sub>-C<sub>6</sub> alkylene" preferably refers to an alkylene group, as defined above, which contains at least 1, and at most 6, carbon atoms respectively. Examples of "C<sub>1</sub>-C<sub>6</sub> alkylene" groups useful in the present invention include, but are not limited to, methylene, ethylene and n-propylene.

25

As used herein, the term "halogen" or "hal" preferably refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

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As used herein, the term "C<sub>1</sub>-C<sub>6</sub> haloalkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms substituted with at least one halogen, halogen being as defined herein.

5 Examples of branched or straight chained "C<sub>1</sub>-C<sub>6</sub> haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo and iodo.

10 As used herein, the term "C<sub>3</sub>-C<sub>7</sub> cycloalkyl" preferably refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms and which optionally includes a C<sub>1</sub>-C<sub>6</sub> alkyl linker through which it may be attached. The C<sub>1</sub>-C<sub>6</sub> alkyl group is as defined above. Exemplary "C<sub>3</sub>-C<sub>7</sub> cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

15 As used herein, the term "C<sub>3</sub>-C<sub>7</sub> cycloalkylene" preferably refers to a non-aromatic alicyclic divalent hydrocarbon radical having from three to seven carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower  
20 alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of  
25 "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

30 As used herein, the term "heterocyclic" or the term "heterocyclyl" preferably refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO<sub>2</sub>, O or N, optionally substituted with substituents selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>

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haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylsulfanyl, C<sub>1</sub>-C<sub>6</sub> haloalkylsulfanyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfenyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, pyrrolidine, piperidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "heterocyclylene" preferably refers to a three to twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO<sub>2</sub>, O or N, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like.

As used herein, the term "aryl" preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or naphthalene ring systems. Exemplary optional substituents include C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub>

alkylsulfanyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfenyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. Examples of "aryl" groups include, but are not limited to Phenyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof.

As used herein, the term "arylene" preferably refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "aralkyl" preferably refers to an aryl or heteroaryl group, as defined herein, attached through a C<sub>1</sub>-C<sub>6</sub> alkyl linker, wherein C<sub>1</sub>-C<sub>6</sub> alkyl is as defined herein. Examples of "aralkyl" include, but are not limited to, benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 5-methyl-3-isoxazolylmethyl and 2-imidazolethyl.

As used herein, the term "heteroaryl" preferably refers to a monocyclic five to seven-membered aromatic ring, or to a fused bicyclic aromatic ring system comprising two of such monocyclic five to seven-membered aromatic rings. These heteroaryl rings contain one or more nitrogen, sulfur

and/or oxygen heteroatoms, where N-Oxides and sulfur Oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted with up to three members selected from a group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylsulfanyl, C<sub>1</sub>-C<sub>6</sub> haloalkylsulfanyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfenyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, heteroaryl or aryl, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, and substituted versions thereof.

As used herein, the term "heteroarylene" preferably refers to a five - to seven -membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-Oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-



2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

5 As used herein, the term "alkoxy" preferably refers to the group  $R_aO-$ , where  $R_a$  is alkyl as defined above and the term " $C_1-C_6$  alkoxy" preferably refers to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary  $C_1-C_6$  alkoxy groups useful in the present invention include, but are not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy.

10 As used herein, the term "haloalkoxy" preferably refers to the group  $R_aO-$ , where  $R_a$  is haloalkyl as defined above and the term " $C_1-C_6$  haloalkoxy" preferably refers to an haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1 and at most 6 carbon atoms.

15 Exemplary  $C_1-C_6$  haloalkoxy groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy substituted with one or more halo groups, for instance trifluoromethoxy.

20 As used herein the term "aralkoxy" preferably refers to the group  $R_C R_B O-$ , where  $R_B$  is alkyl and  $R_C$  is aryl as defined above.

As used herein the term "aryloxy" preferably refers to the group  $R_C O-$ , where  $R_C$  is aryl as defined above.

25 As used herein, the term "alkylsulfanyl" preferably refers to the group  $R_A S-$ , where  $R_A$  is alkyl as defined above and the term " $C_1-C_6$  alkylsulfanyl" preferably refers to an alkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

30 As used herein, the term "haloalkylsulfanyl" preferably refers to the group  $R_D S-$ , where  $R_D$  is haloalkyl as defined above and the term " $C_1-C_6$

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haloalkylsulfanyl" preferably refers to a haloalkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 2 and at most 6 carbon atoms.

5 As used herein, the term "alkylsulfenyl" preferably refers to the group  $R_A S(O)-$ , where  $R_A$  is alkyl as defined above and the term " $C_1-C_6$  alkylsulfenyl" preferably refers to an alkylsulfenyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

10 As used herein, the term "alkylsulfonyl" preferably refers to the group  $R_A SO_2-$ , where  $R_A$  is alkyl as defined above and the term " $C_1-C_6$  alkylsulfonyl" preferably refers to an alkylsulfonyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

15 As used herein, the term "oxo" preferably refers to the group  $=O$ .

As used herein, the term "mercapto" preferably refers to the group  $-SH$ .

As used herein, the term "carboxy" preferably refers to the group  $-COOH$ .

20

As used herein, the term "cyano" preferably refers to the group  $-CN$ .

As used herein, the term "cyanoalkyl" preferably refers to the group  $-R_B CN$ , wherein  $R_B$  is alkyl as defined above. Exemplary "cyanoalkyl" groups useful in the present invention include, but are not limited to, cyanomethyl, cyanoethyl and cyanoisopropyl.

25

As used herein, the term "aminosulfonyl" preferably refers to the group  $-SO_2NH_2$ .

30

As used herein, the term "carbamoyl" preferably refers to the group  $-C(O)NH_2$ .

- 30 -

As used herein, the term "sulfanyl" shall refer to the group -S-.

As used herein, the term "sulfenyl" shall refer to the group -S(O)-.

5

As used herein, the term "sulfonyl" shall refer to the group -S(O)<sub>2</sub>- or -SO<sub>2</sub>-.

10

As used herein, the term "acyl" preferably refers to the group R<sub>F</sub>C(O)-, where R<sub>F</sub> is alkyl, cycloalkyl or heterocyclyl as defined herein.

As used herein, the term "aroyl" preferably refers to the group R<sub>C</sub>C(O)-, where R<sub>C</sub> is aryl as defined herein.

15

As used herein, the term "heteroaroyl" preferably refers to the group R<sub>E</sub>C(O)-, where R<sub>E</sub> is heteroaryl as defined herein.

As used herein, the term "alkoxycarbonyl" preferably refers to the group R<sub>A</sub>OC(O)-, where R<sub>A</sub> is alkyl as defined herein.

20

As used herein, the term "acyloxy" preferably refers to the group R<sub>F</sub>C(O)O-, where R<sub>F</sub> is alkyl, cycloalkyl, or heterocyclyl as defined herein.

As used herein, the term "aroyloxy" preferably refers to the group R<sub>C</sub>C(O)O-, where R<sub>C</sub> is aryl as defined herein.

25

As used herein, the term "heteroaroyloxy" preferably refers to the group R<sub>E</sub>C(O)O-, where R<sub>E</sub> is heteroaryl as defined herein.

30

As used herein, the term "carbonyl" or "carbonyl moiety" preferably refers to the group C=O.

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As used herein, the term "thiocarbonyl" or "thiocarbonyl moiety" preferably refers to the group C=S.

5 As used herein, the term "amino", "amino group" or "amino moiety" preferably refers to the group  $\text{NR}_\text{G}\text{R}_\text{G}'$ , wherein  $\text{R}_\text{G}$  and  $\text{R}_\text{G}'$  are preferably selected, independently from one another, from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylencycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If both  $\text{R}_\text{G}$  and  $\text{R}_\text{G}'$  are hydrogen,  $\text{NR}_\text{G}\text{R}_\text{G}'$  is also referred to as "unsubstituted amino moiety" or  
10 "unsubstituted amino group". If  $\text{R}_\text{G}$  and/or  $\text{R}_\text{G}'$  are other than hydrogen,  $\text{NR}_\text{G}\text{R}_\text{G}'$  is also referred to as "substituted amino moiety" or "substituted amino group".

15 As used herein, the term "imino" or "imino moiety" preferably refers to the group  $\text{C}=\text{NR}_\text{G}$ , wherein  $\text{R}_\text{G}$  is preferably selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylencycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If  $\text{R}_\text{G}$  is hydrogen,  $\text{C}=\text{NR}_\text{G}$  is also referred to as "unsubstituted imino moiety". If  $\text{R}_\text{G}$  is a residue other than hydrogen,  $\text{C}=\text{NR}_\text{G}$  is also referred to as "substituted  
20 imino moiety".

25 As used herein, the term "ethene-1,1-diyl moiety" preferably refers to the group  $\text{C}=\text{CR}_\text{K}\text{R}_\text{L}$ , wherein  $\text{R}_\text{K}$  and  $\text{R}_\text{L}$  are preferably selected, independently from one another, from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, nitro, alkylencycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If both hydrogen  $\text{R}_\text{K}$  and  $\text{R}_\text{L}$  are hydrogen,  $\text{C}=\text{CR}_\text{K}\text{R}_\text{L}$  is also referred to as "unsubstituted ethene-1,1-diyl moiety". If one of  $\text{R}_\text{K}$  and  $\text{R}_\text{L}$  or both are a residue other than hydrogen,  $\text{C}=\text{CR}_\text{K}\text{R}_\text{L}$  is also referred to as "substituted ethene-1,1-diyl moiety".  
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As used herein, the terms "group", "residue" and "radical" or "groups", "residues" and "radicals" are usually used as synonyms, respectively, as it is common practice in the art.

5 As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

10 As used herein, the term "physiologically functional derivative" preferably refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue  
15 experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

20 As used herein, the term "solvate" preferably refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I or formula II or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable  
25 solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

30

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As used herein, the term "substituted" preferably refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

5 Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two or more stereoisomers, which are usually enantiomers and/or diastereomers. Accordingly, the compounds of this invention include mixtures of stereoisomers, especially mixtures of enantiomers, as well as purified  
10 stereoisomers, especially purified enantiomers, or stereoisomerically enriched mixtures, especially enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formulae I and II above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers  
15 the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral Centers are inverted. Also, it is understood that all tautomers and mixtures of tautomers of the compounds of formulae (I) or (II) are included within the scope of the compounds of formulae (I) and (II) and preferably the  
20 formulae and subformulae corresponding thereto.

Racemates obtained can be resolved into the isomers mechanically or chemically by methods known per se. Diastereomers are preferably formed from the racemic mixture by reaction with an optically active  
25 resolving agent. Examples of suitable resolving agents are optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids, such as  $\beta$ -camphorsulfonic acid. Also advantageous is enantiomer resolution with the aid of a column filled  
30 with an optically active resolving agent (for example dinitrobenzoylphenyl-

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glycine); an example of a suitable eluent is a hexane/isopropanol/  
acetonitrile mixture.

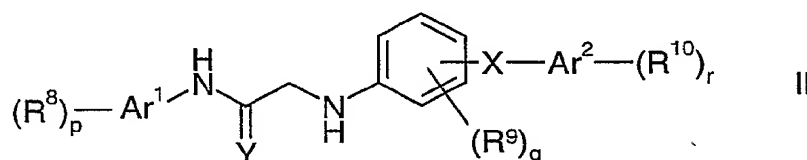
5 The diastereomer resolution can also be carried out by standard  
purification processes, such as, for example, chromatography or fractional  
crystallization.

10 It is of course also possible to obtain optically active compounds of the  
formula I or II by the methods described above by using starting materials  
which are already optically active.

Unless indicated otherwise, it is to be understood that reference to  
compounds of formula I preferably includes the reference to the  
compounds formulae Ia to Id and/or of formula II. Unless indicated  
15 otherwise, it is to be understood that reference to the compounds of  
formula II preferably includes the reference to the sub formulae  
corresponding thereto, for example the sub formulae II.1 to II.20 and  
preferably formulae IIa to IIh. It is also understood that the following  
embodiments, including uses and compositions, although recited with  
20 respect to formula I are preferably also applicable to formulae II, sub  
formulae II.1 to II.20 and preferably formulae IIa to IIh.

Especially preferred compounds according to the invention are compounds  
of formula II

25



30

wherein

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- Ar<sup>1</sup>, Ar<sup>2</sup> are selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,
- R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, C(Hal)<sub>3</sub>, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CN, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>OR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>k</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COOR<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>COR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>SO<sub>2</sub>A, (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>OC(O)R<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>SR<sup>11</sup>, CH=N-OA, CH<sub>2</sub>CH=N-OA, (CH<sub>2</sub>)<sub>n</sub>NHOA, (CH<sub>2</sub>)<sub>n</sub>CH=N-R<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>OC(O)NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>COOR<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>N(R<sup>11</sup>)CH<sub>2</sub>CH<sub>2</sub>OR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>N(R<sup>11</sup>)CH<sub>2</sub>CH<sub>2</sub>OCF<sub>3</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sup>11</sup>)C(R<sup>13</sup>)HCOOR<sup>12</sup>, C(R<sup>13</sup>)HCOR<sup>14</sup>, (CH<sub>2</sub>)<sub>n</sub>N(R<sup>11</sup>)CH<sub>2</sub>CH<sub>2</sub>N(R<sup>12</sup>)CH<sub>2</sub>COOR<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>N(R<sup>11</sup>)CH<sub>2</sub>CH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, CH=CHCOOR<sup>11</sup>, CH=CHCH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, CH=CHCH<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, CH=CHCH<sub>2</sub>OR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>N(COOR<sup>11</sup>)COOR<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>N(CONH<sub>2</sub>)COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>N(CONH<sub>2</sub>)CONH<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>N(CH<sub>2</sub>COOR<sup>11</sup>)COOR<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>N(CH<sub>2</sub>CONH<sub>2</sub>)COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>N(CH<sub>2</sub>CONH<sub>2</sub>)CONH<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CHR<sup>13</sup>COR<sup>14</sup>, (CH<sub>2</sub>)<sub>n</sub>CHR<sup>13</sup>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CHR<sup>13</sup>CH<sub>2</sub>OR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>OCN and (CH<sub>2</sub>)<sub>n</sub>NCO, wherein
- R<sup>11</sup>, R<sup>12</sup> are independently selected from a group consisting of H, A, (CH<sub>2</sub>)<sub>m</sub>Ar<sup>3</sup> and (CH<sub>2</sub>)<sub>m</sub>Het, or in NR<sup>11</sup>R<sup>12</sup>,



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- 5  $R^{11}$  and  $R^{12}$  form, together with the N-Atom they are bound to, a 5-, 6- or 7-membered heterocyclus which additionally contains 1 or 2 hetero atoms, selected from N, O an S,
- $R^{13}$ ,  $R^{14}$  are independently selected from a group consisting of H, Hal, A,  $(CH_2)_mAr^4$  and  $(CH_2)_mHet$ ,
- 10 A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylencycloalkyl, alkoxy and alkoxyalkyl,
- $Ar^3$ ,  $Ar^4$  are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal,  $NO_2$ , CN,  $OR^{15}$ ,  $NR^{15}R^{16}$ ,  $COOR^{15}$ ,  $CONR^{15}R^{16}$ ,  $NR^{15}COR^{16}$ ,  $NR^{15}CONR^{15}R^{16}$ ,  $NR^{16}SO_2A$ ,  $COR^{15}$ ,  $SO_2R^{15}R^{16}$ ,  $S(O)_uA$  and  $OOCR^{15}$ ,
- 15
- 20 Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one ore more substituents, selected from a group consisting of A, Hal,  $NO_2$ , CN,  $OR^{15}$ ,  $NR^{15}R^{16}$ ,  $COOR^{15}$ ,  $CONR^{15}R^{16}$ ,  $NR^{15}COR^{16}$ ,  $NR^{15}CONR^{15}R^{16}$ ,  $NR^{16}SO_2A$ ,  $COR^{15}$ ,  $SO_2R^{15}R^{16}$ ,  $S(O)_uA$  and  $OOCR^{15}$ ,
- 25
- $R^{15}$ ,  $R^{16}$  are independently selected from a group consisting of H, A, and  $(CH_2)_mAr^6$ , wherein
- 30  $Ar^6$  is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents

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selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH<sub>2</sub> and CF<sub>3</sub>,

- 5 k, m and n are independently of one another 0, 1, 2, 3, 4, or 5,
- X represents a bond or is (CR<sup>11</sup>R<sup>12</sup>)<sub>h</sub>, or (CHR<sup>11</sup>)<sub>h</sub>-Q-(CHR<sup>12</sup>)<sub>i</sub>, wherein
- 10 Q is selected from a group consisting of O, S, N-R<sup>15</sup>, (CHal<sub>2</sub>)<sub>j</sub>, (O-CHR<sup>18</sup>)<sub>j</sub>, (CHR<sup>18</sup>-O)<sub>j</sub>, CR<sup>18</sup>=CR<sup>19</sup>, (O-CHR<sup>18</sup>CHR<sup>19</sup>)<sub>j</sub>, (CHR<sup>18</sup>CHR<sup>19</sup>-O)<sub>j</sub>, C=O, C=S, C=NR<sup>15</sup>, CH(OR<sup>15</sup>), C(OR<sup>15</sup>)(OR<sup>20</sup>), C(=O)O, OC(=O), OC(=O)O, C(=O)N(R<sup>15</sup>), N(R<sup>15</sup>)C(=O), OC(=O)N(R<sup>15</sup>), N(R<sup>15</sup>)C(=O)O, CH=N-O, CH=N-NR<sup>15</sup>, S=O, SO<sub>2</sub>, SO<sub>2</sub>NR<sup>15</sup> and NR<sup>15</sup>SO<sub>2</sub>, wherein
- 15 R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> are independently selected from the meanings given for R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup>, preferably independently selected from the group consisting of H, A, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, C(Hal)<sub>3</sub>, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CN, (CH<sub>2</sub>)<sub>n</sub>OR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>k</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>COR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>SO<sub>2</sub>A, (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>SR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>NHOA and (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>COOR<sup>12</sup>,
- 20 25
- h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6, and
- 30 j is 1, 2, 3, 4, 5, or 6,

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- Y is selected from O, S,  $\text{NR}^{21}$ ,  $\text{C}(\text{R}^{22})\text{-NO}_2$ ,  $\text{C}(\text{R}^{22})\text{-CN}$  and  $\text{C}(\text{CN})_2$ , wherein
- 5  $\text{R}^{21}$  is independently selected from the meanings given for  $\text{R}^{13}$ ,  $\text{R}^{14}$  and
- $\text{R}^{22}$  is independently selected from the meanings given for  $\text{R}^{11}$ ,  $\text{R}^{12}$ ,
- 10 p, r are independently from one another 0, 1, 2, 3, 4 or 5,
- q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,
- 15 u is 0, 1, 2 or 3, preferably 0, 1 or 2,
- and
- Hal is independently selected from a group consisting of F, Cl, Br and I;
- 20 and the salts and solvates thereof, preferably the physiologically acceptable salts and solvates thereof.
- Even more preferred are compounds of formula II
- 25 wherein
- $\text{Ar}^1$ ,  $\text{Ar}^2$  are selected independently from one another from aromatic hydrocarbons containing 6 to 10 and especially
- 30 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two

heteroatoms, independently selected from N, O and S and especially selected from N and O,

5  $R^8$ ,  $R^9$  and  $R^{10}$  are independently selected from a group consisting of H, A, cycloalkyl 3 to 7 carbon atoms, Hal,  $CH_2Hal$ ,  $CH(Hal)_2$ ,  $C(Hal)_3$ ,  $NO_2$ ,  $(CH_2)_nCN$ ,  $(CH_2)_nOR^{11}$ ,  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $(CH_2)_nCOOR^{11}$ ,  $(CH_2)_nCONR^{11}R^{12}$ ,  $(CH_2)_nNR^{11}COR^{13}$ ,  $(CH_2)_nNR^{11}CONR^{11}R^{12}$ ,  $(CH_2)_nNR^{11}SO_2A$ ,  $(CH_2)_nSO_2NR^{11}R^{12}$ ,  $(CH_2)_nS(O)_uR^{13}$ ,  $(CH_2)_nOC(O)R^{13}$ ,  $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nSR^{11}$ ,  $(CH_2)_nNHOA$ ,  $(CH_2)_nNR^{11}COOR^{12}$ ,  $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$ ,  $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$ ,  $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$ ,  $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{13}$ ,  $(CH_2)_nN(COOR^{13})COOR^{14}$ ,  $(CH_2)_nN(CONH_2)COOR^{11}$ ,  $(CH_2)_nN(CONH_2)CONH_2$ ,  $(CH_2)_nN(CH_2COOR^{11})COOR^{12}$ ,  $(CH_2)_nN(CH_2CONH_2)COOR^{11}$ ,  $(CH_2)_nN(CH_2CONH_2)CONH_2$ ,  $(CH_2)_nCHR^{13}COR^{14}$ ,  $(CH_2)_nCHR^{13}COOR^{12}$  and  $(CH_2)_nCHR^{13}CH_2OR^{14}$ ,

10  $X$  represents a bond or is  $(CR^{11}R^{12})_h$ , or  $(CHR^{11})_h-Q$  or  $(CHR^{12})_i$ , wherein

15  $Q$  is selected from a group consisting of O, S,  $N-R^{15}$ ,  $(CHal_2)_j$ ,  $(O-CHR^{18})_j$ ,  $(CHR^{18}-O)_j$ ,  $CR^{18}=CR^{19}$ ,  $(O-CHR^{18}CHR^{19})_j$ ,  $(CHR^{18}CHR^{19}-O)_j$ ,  $C=O$ ,  $C=NR^{15}$ ,  $CH(OR^{15})$ ,  $C(OR^{15})(OR^{20})$ ,  $C(=O)N(R^{15})$ ,  $N(R^{15})C(=O)$ ,  $CH=N-NR^{15}$ ,  $S=O$ ,  $SO_2$ ,  $SO_2NR^{15}$  and  $NR^{15}SO_2$ ,

20 wherein

25  $n$  is an integer from 0 to 10,  $k$  is an integer from 0 to 10,  $u$  is an integer from 0 to 10,  $h$  is an integer from 0 to 10,  $i$  is an integer from 0 to 10,  $j$  is an integer from 0 to 10,  $A$  is a substituent, and  $OR^{15}$ ,  $OR^{20}$ ,  $NR^{15}$ ,  $NR^{16}$ ,  $NR^{17}$ ,  $NR^{18}$ ,  $NR^{19}$ ,  $NR^{20}$ ,  $NR^{21}$ ,  $NR^{22}$ ,  $NR^{23}$ ,  $NR^{24}$ ,  $NR^{25}$ ,  $NR^{26}$ ,  $NR^{27}$ ,  $NR^{28}$ ,  $NR^{29}$ ,  $NR^{30}$ ,  $NR^{31}$ ,  $NR^{32}$ ,  $NR^{33}$ ,  $NR^{34}$ ,  $NR^{35}$ ,  $NR^{36}$ ,  $NR^{37}$ ,  $NR^{38}$ ,  $NR^{39}$ ,  $NR^{40}$ ,  $NR^{41}$ ,  $NR^{42}$ ,  $NR^{43}$ ,  $NR^{44}$ ,  $NR^{45}$ ,  $NR^{46}$ ,  $NR^{47}$ ,  $NR^{48}$ ,  $NR^{49}$ ,  $NR^{50}$ ,  $NR^{51}$ ,  $NR^{52}$ ,  $NR^{53}$ ,  $NR^{54}$ ,  $NR^{55}$ ,  $NR^{56}$ ,  $NR^{57}$ ,  $NR^{58}$ ,  $NR^{59}$ ,  $NR^{60}$ ,  $NR^{61}$ ,  $NR^{62}$ ,  $NR^{63}$ ,  $NR^{64}$ ,  $NR^{65}$ ,  $NR^{66}$ ,  $NR^{67}$ ,  $NR^{68}$ ,  $NR^{69}$ ,  $NR^{70}$ ,  $NR^{71}$ ,  $NR^{72}$ ,  $NR^{73}$ ,  $NR^{74}$ ,  $NR^{75}$ ,  $NR^{76}$ ,  $NR^{77}$ ,  $NR^{78}$ ,  $NR^{79}$ ,  $NR^{80}$ ,  $NR^{81}$ ,  $NR^{82}$ ,  $NR^{83}$ ,  $NR^{84}$ ,  $NR^{85}$ ,  $NR^{86}$ ,  $NR^{87}$ ,  $NR^{88}$ ,  $NR^{89}$ ,  $NR^{90}$ ,  $NR^{91}$ ,  $NR^{92}$ ,  $NR^{93}$ ,  $NR^{94}$ ,  $NR^{95}$ ,  $NR^{96}$ ,  $NR^{97}$ ,  $NR^{98}$ ,  $NR^{99}$ ,  $NR^{100}$ ,  $NR^{101}$ ,  $NR^{102}$ ,  $NR^{103}$ ,  $NR^{104}$ ,  $NR^{105}$ ,  $NR^{106}$ ,  $NR^{107}$ ,  $NR^{108}$ ,  $NR^{109}$ ,  $NR^{110}$ ,  $NR^{111}$ ,  $NR^{112}$ ,  $NR^{113}$ ,  $NR^{114}$ ,  $NR^{115}$ ,  $NR^{116}$ ,  $NR^{117}$ ,  $NR^{118}$ ,  $NR^{119}$ ,  $NR^{120}$ ,  $NR^{121}$ ,  $NR^{122}$ ,  $NR^{123}$ ,  $NR^{124}$ ,  $NR^{125}$ ,  $NR^{126}$ ,  $NR^{127}$ ,  $NR^{128}$ ,  $NR^{129}$ ,  $NR^{130}$ ,  $NR^{131}$ ,  $NR^{132}$ ,  $NR^{133}$ ,  $NR^{134}$ ,  $NR^{135}$ ,  $NR^{136}$ ,  $NR^{137}$ ,  $NR^{138}$ ,  $NR^{139}$ ,  $NR^{140}$ ,  $NR^{141}$ ,  $NR^{142}$ ,  $NR^{143}$ ,  $NR^{144}$ ,  $NR^{145}$ ,  $NR^{146}$ ,  $NR^{147}$ ,  $NR^{148}$ ,  $NR^{149}$ ,  $NR^{150}$ ,  $NR^{151}$ ,  $NR^{152}$ ,  $NR^{153}$ ,  $NR^{154}$ ,  $NR^{155}$ ,  $NR^{156}$ ,  $NR^{157}$ ,  $NR^{158}$ ,  $NR^{159}$ ,  $NR^{160}$ ,  $NR^{161}$ ,  $NR^{162}$ ,  $NR^{163}$ ,  $NR^{164}$ ,  $NR^{165}$ ,  $NR^{166}$ ,  $NR^{167}$ ,  $NR^{168}$ ,  $NR^{169}$ ,  $NR^{170}$ ,  $NR^{171}$ ,  $NR^{172}$ ,  $NR^{173}$ ,  $NR^{174}$ ,  $NR^{175}$ ,  $NR^{176}$ ,  $NR^{177}$ ,  $NR^{178}$ ,  $NR^{179}$ ,  $NR^{180}$ ,  $NR^{181}$ ,  $NR^{182}$ ,  $NR^{183}$ ,  $NR^{184}$ ,  $NR^{185}$ ,  $NR^{186}$ ,  $NR^{187}$ ,  $NR^{188}$ ,  $NR^{189}$ ,  $NR^{190}$ ,  $NR^{191}$ ,  $NR^{192}$ ,  $NR^{193}$ ,  $NR^{194}$ ,  $NR^{195}$ ,  $NR^{196}$ ,  $NR^{197}$ ,  $NR^{198}$ ,  $NR^{199}$ ,  $NR^{200}$ ,  $NR^{201}$ ,  $NR^{202}$ ,  $NR^{203}$ ,  $NR^{204}$ ,  $NR^{205}$ ,  $NR^{206}$ ,  $NR^{207}$ ,  $NR^{208}$ ,  $NR^{209}$ ,  $NR^{210}$ ,  $NR^{211}$ ,  $NR^{212}$ ,  $NR^{213}$ ,  $NR^{214}$ ,  $NR^{215}$ ,  $NR^{216}$ ,  $NR^{217}$ ,  $NR^{218}$ ,  $NR^{219}$ ,  $NR^{220}$ ,  $NR^{221}$ ,  $NR^{222}$ ,  $NR^{223}$ ,  $NR^{224}$ ,  $NR^{225}$ ,  $NR^{226}$ ,  $NR^{227}$ ,  $NR^{228}$ ,  $NR^{229}$ ,  $NR^{230}$ ,  $NR^{231}$ ,  $NR^{232}$ ,  $NR^{233}$ ,  $NR^{234}$ ,  $NR^{235}$ ,  $NR^{236}$ ,  $NR^{237}$ ,  $NR^{238}$ ,  $NR^{239}$ ,  $NR^{240}$ ,  $NR^{241}$ ,  $NR^{242}$ ,  $NR^{243}$ ,  $NR^{244}$ ,  $NR^{245}$ ,  $NR^{246}$ ,  $NR^{247}$ ,  $NR^{248}$ ,  $NR^{249}$ ,  $NR^{250}$ ,  $NR^{251}$ ,  $NR^{252}$ ,  $NR^{253}$ ,  $NR^{254}$ ,  $NR^{255}$ ,  $NR^{256}$ ,  $NR^{257}$ ,  $NR^{258}$ ,  $NR^{259}$ ,  $NR^{260}$ ,  $NR^{261}$ ,  $NR^{262}$ ,  $NR^{263}$ ,  $NR^{264}$ ,  $NR^{265}$ ,  $NR^{266}$ ,  $NR^{267}$ ,  $NR^{268}$ ,  $NR^{269}$ ,  $NR^{270}$ ,  $NR^{271}$ ,  $NR^{272}$ ,  $NR^{273}$ ,  $NR^{274}$ ,  $NR^{275}$ ,  $NR^{276}$ ,  $NR^{277}$ ,  $NR^{278}$ ,  $NR^{279}$ ,  $NR^{280}$ ,  $NR^{281}$ ,  $NR^{282}$ ,

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h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6,  
preferably 0, 1, 2 or 3 and

j is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,

p is 1, 2, 3 or 4, preferably 1, 2 or 3, and

r is 0, 1, 2, or 3, preferably 0, 1 or 2;

and the salts and solvates thereof, preferably the physiologically  
acceptable salts and solvates thereof.

Subject of the present invention are especially compounds of formula I and  
II, in which one or more substituents or groups, preferably the major part of  
the substituents or groups has a meaning which is indicated as preferred,  
more preferred, even more preferred or especially preferred.

In compounds of formula II, the term alkyl preferably refers to an  
unbranched or branched alkyl residue, preferably an unbranched alkyl  
residue comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, preferably 1, 2, 3, 4, 5 or  
6, more preferred 1, 2, 3 or 4 and especially 1 or 2 carbon atoms, or a  
branched alkyl residue comprising 3, 4, 5, 6, 7, 8, 9 or 10, preferably 3, 4,  
5 or 6 more preferred 3 or 4 carbon atoms. The alkyl residues can be  
optionally substituted, especially by one or more halogen atoms, for  
example up to perhaloalkyl, by one or more hydroxy groups or by one or  
more amino groups, all of which can optionally be substituted by alkyl. If an  
alkyl residue is substituted by halogen, it usually comprises 1, 2, 3, 4 or 5  
halogen atoms, depending on the number of carbon atoms of the alkyl  
residue. For example, a methyl group can comprise, 1, 2 or 3 halogen  
atoms, an ethyl group (an alkyl residue comprising 2 carbon atoms) can  
comprise 1, 2, 3, 4 or 5 halogen atoms. If an alkyl residue is substituted by  
hydroxy groups, it usually comprises one or two, preferably one hydroxy

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groups. If the hydroxy group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. If an alkyl residue is substituted by amino groups, it usually comprises one or two, preferably one amino groups. If the amino group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. According to compounds of formula II, alkyl is preferably selected from the group consisting of methyl, ethyl, trifluoro methyl, pentafluoro ethyl, isopropyl, tert.-butyl, 2-amino ethyl, N-methyl-2-amino ethyl, N,N-dimethyl-2-amino ethyl, N-ethyl-2-amino ethyl, N,N-diethyl-2-amino ethyl, 2-hydroxy ethyl, 2-methoxy ethyl and 2-ethoxy ethyl, further preferred of the group consisting of 2-butyl, n-pentyl, neo-pentyl, isopentyl, hexyl and n-decyl, more preferred of methyl, ethyl, trifluoro methyl, isopropyl and tert.-butyl.

In compounds of formula II, alkenyl is preferably selected from the group consisting of allyl, 2- or 3-butenyl, isobutenyl, sec-butenyl, furthermore preferably 4-pentenyl, isopentenyl and 5-hexenyl.

In compounds of formula II, alkylene is preferably unbranched and is more preferably methylene or ethylene, furthermore preferably propylene or butylene.

In compounds of formula II, alkylencycloalkyl preferably has 5 to 10 carbon atoms and is preferably methylenecyclopropyl, methylenecyclobutyl, furthermore preferably methylenecyclopentyl, methylenecyclohexyl or methylenecycloheptyl, furthermore alternatively ethylenecyclopropyl, ethylenecyclobutyl, ethylenecyclopentyl, ethylenecyclohexyl or ethylenecycloheptyl, propylenecyclopentyl, propylenecyclohexyl, butylenecyclopentyl or butylenecyclohexyl.

In compounds of formula II, the term "alkoxy" preferably comprises groups of formula O-alkyl, where alkyl is an alkyl group as defined above. More preferred, alkoxy is selected from group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, 2-butoxy, tert.-butoxy and halogenated, especially perhalogenated, derivatives thereof. Preferred perhalogenated derivatives are selected from the group consisting of O-CCl<sub>3</sub>, O-CF<sub>3</sub>, O-C<sub>2</sub>Cl<sub>5</sub>, O-C<sub>2</sub>F<sub>5</sub>, O-C(CCl<sub>3</sub>)<sub>3</sub> and O-C(CF<sub>3</sub>)<sub>3</sub>.

In compounds of formula II, the term "alkoxyalkyl" preferably comprises branched and unbranched residues, more preferred unbranched residues, of formula C<sub>u</sub>H<sub>2u+1</sub>-O-(CH<sub>2</sub>)<sub>v</sub>, wherein u and v are independently from each other 1 to 6. Especially preferred is u = 1 and v = 1 to 4.

In compounds of formula II the term "alkoxyalkyl" includes alkoxyalkyl groups as defined above, wherein one or more of the hydrogen atoms are substituted by halogen, for example up to perhalo alkoxyalkyl.

In compounds of formula II, cycloalkyl preferably has 3 – 7 carbon atoms and is preferably cyclopropyl or cyclobutyl, furthermore preferably cyclopentyl or cyclohexyl, furthermore also cycloheptyl, particularly preferably cyclopentyl.

In compounds of formula II, Ar<sup>3</sup> to Ar<sup>6</sup> are preferably selected independently from one another from phenyl, naphthyl and biphenyl which is optionally substituted by one or more substituents, selected from the group consisting of A, Hal, NO<sub>2</sub>, CN, OR<sup>15</sup>, NR<sup>15</sup>R<sup>16</sup>, COOR<sup>15</sup>, CONR<sup>15</sup>R<sup>16</sup>, NR<sup>15</sup>COR<sup>16</sup>, NR<sup>15</sup>CONR<sup>15</sup>R<sup>16</sup>, NR<sup>16</sup>SO<sub>2</sub>A, COR<sup>15</sup>, SO<sub>2</sub>R<sup>15</sup>R<sup>16</sup>, S(O)<sub>u</sub>A and OOCR<sup>15</sup>.

In compounds of formula II, het is preferably an optionally substituted aromatic heterocyclic residue and even more preferred and optionally substituted saturated heterocyclic residue, wherein the substituents are

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preferably selected from A, CN and Hal. Even more preferred, het is selected from the group consisting of 1-piperidyl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 4-morpholinyl, 1-4pyrrolidinyl, 1-pyrazolidinyl 1-(2-methyl)-pyrazolidinyl, 1-imidazolidinyl or 1-(3-methyl)-imidazolidinyl, thiophen-2-yl, thiophen-3-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, chinolinyl, isochinolinyl, 2-pyridazyl, 4-pyridazyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 2-pyrazinyl and 3-pyrazinyl.

10 Preferably, the sum of h and l exceeds 0.

A preferred aspect of the instant invention relates to compounds of formula II, wherein n is 0 or 1 and especially 0.

15 Another preferred aspect of the instant invention relates to compounds of formula II, wherein n is 0 in the residues  $R^8$ ,  $R^9$  and/or  $R^{10}$  and especially in  $R^{10}$ .

Another preferred aspect of the instant invention relates to compounds of formula II, wherein X represents a bridging group, selected from  $(CR^{11}R^{12})_h$  or  $(CHR^{11})_h-Q-(CHR^{12})_l$ .

20 The invention relates in particular to compounds of the formula II in which at least one of said radicals has one of the preferred meanings given above.

Some mere preferred groups of compounds may be expressed by the following sub-formulae II.1) to II.20), which correspond to the formula II and in which radicals not denoted in greater detail are as defined in the formula II, but in which



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- II.1) Ar<sup>1</sup> is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl;
- 5 II.2) Ar<sup>1</sup> is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl, and
- p is 1, 3 or 3;
- 10 II.3) Ar<sup>1</sup> is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- 15 p is 1, 2 or 3, and
- R<sup>8</sup> is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, perhaloalkyl comprising 1 to 4 carbon atoms, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CN, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup> and (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>;
- 20
- II.4) Ar<sup>1</sup> is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- 25
- p is 1, 2 or 3,
- 30 R<sup>8</sup> is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, perhaloalkyl comprising

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1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  
 $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  
 $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$  and  $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$ ;

5      II.5)     $\text{Ar}^1$       is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or  
 imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and  
 especially phenyl or oxazolyl,

10                     $p$       is 1, 2 or 3,

$\text{R}^8$       is selected from the group consisting of alkyl comprising  
 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon  
 atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH}(\text{Hal})_2$ , perhaloalkyl comprising  
 1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  
 15                     $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  
 $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$  and  $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$ , wherein

$n$       is 0 or 1;

20      II.6)     $\text{Ar}^1$       is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or  
 imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and  
 especially phenyl or oxazolyl,

25                     $p$       is 1, 2 or 3,

$\text{R}^8$       is selected from the group consisting of alkyl comprising  
 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon  
 atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH}(\text{Hal})_2$ , perhaloalkyl comprising  
 1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  
 30                     $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  
 $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$  and  $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$ , wherein

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- n is 0 or 1, and
- u is 0;
- 5 II.7) Ar<sup>1</sup> is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- p is 1, 2 or 3,
- 10 R<sup>8</sup> is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, perhaloalkyl comprising 1 to 4 carbon atoms, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CN, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>,  
15 (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup> and (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>, wherein
- n is 0 or 1,
- 20 u is 0 or 2, preferably 0, and
- q is 0 or 1, and
- 25 X is selected from the group consisting of O, S, NR<sup>15</sup>, CHOR<sup>11</sup>, CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>, OCH<sub>2</sub>, CH<sub>2</sub>O, OCH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>O, preferably O, S and CH<sub>2</sub> and especially O and S;
- 30 II.8) Ar<sup>1</sup> is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,

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- p is 1, 2 or 3,
- 5  $R^8$  is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $CH_2Hal$ ,  $CH(Hal)_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $NO_2$ ,  $(CH_2)_nCN$ ,  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nCOOR^{11}$ ,  $(CH_2)_nCONR^{11}R^{12}$ ,  $(CH_2)_nSO_2NR^{11}R^{12}$  and  $(CH_2)_nS(O)_uR^{13}$ , wherein
- 10 n is 0 or 1,
- u is 0 or 2, preferably 0, and
- 15 q is 0 or 1, and
- X is selected from the group consisting of O, S,  $NR^{15}$ ,  $CHOR^{11}$ ,  $CH_2$ ,  $CH_2CH_2$ ,  $OCH_2$ ,  $CH_2O$ ,  $OCH_2CH_2$ ,  $CH_2CH_2O$ , preferably O, S and  $CH_2$  and especially O and S,
- 20  $Ar^2$  is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl;
- 25 II.9)  $Ar^1$  is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- p is 1, 2 or 3,
- 30  $R^8$  is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $CH_2Hal$ ,  $CH(Hal)_2$ , perhaloalkyl comprising

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1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  
 $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  
 $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$  and  $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$ , wherein

5            n            is 0 or 1,

             u            is 0 or 2, preferably 0, and

             q            is 0 or 1, and

10

X            is selected from the group consisting of O, S,  $\text{NR}^{15}$ ,  
 $\text{CHOR}^{11}$ ,  $\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2$ ,  $\text{OCH}_2$ ,  $\text{CH}_2\text{O}$ ,  $\text{OCH}_2\text{CH}_2$ ,  
 $\text{CH}_2\text{CH}_2\text{O}$ , preferably O, S and  $\text{CH}_2$  and especially O  
and S,

15

$\text{Ar}^2$           is phenyl, pyridinyl or pyrimidyl, and especially is phenyl  
or pyridinyl, and

20

$\text{R}^{10}$           is selected from the group consisting of H, alkyl  
comprising 1 to 4 carbon atoms, alkoxy comprising 1 to  
4 carbon atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH}(\text{Hal})_2$ , perhaloalkyl  
comprising 1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  
 $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$   
25            and  $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$ , preferably selected from the group  
consisting of alkyl comprising 1 to 4 carbon atoms,  
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  
 $(\text{CH}_2)_n\text{COOR}^{13}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$  and especially  
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,

30

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- II.10)  $Ar^1$  is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and especially phenyl or oxazolyl,
- 5  $p$  is 1, 2 or 3,
- $R^8$  is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $CH_2Hal$ ,  $CH(Hal)_2$ , perhaloalkyl comprising 10 1 to 4 carbon atoms,  $NO_2$ ,  $(CH_2)_nCN$ ,  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nCOOR^{11}$ ,  $(CH_2)_nCONR^{11}R^{12}$ ,  $(CH_2)_nSO_2NR^{11}R^{12}$  and  $(CH_2)_nS(O)_uR^{13}$ , wherein
- $n$  is 0 or 1,
- 15  $u$  is 0 or 2, preferably 0, and
- $q$  is 0 or 1, and
- 20  $X$  is selected from the group consisting of O, S,  $NR^{15}$ ,  $CHOR^{11}$ ,  $CH_2$ ,  $CH_2CH_2$ ,  $OCH_2$ ,  $CH_2O$ ,  $OCH_2CH_2$ ,  $CH_2CH_2O$ , preferably O, S and  $CH_2$  and especially O and S,
- 25  $Ar^2$  is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- $R^{10}$  is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 30 4 carbon atoms, Hal,  $CH_2Hal$ ,  $CH(Hal)_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $NO_2$ ,  $(CH_2)_nCN$ ,  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $(CH_2)_nCOR^{13}$ ,

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5 (CH<sub>2</sub>)<sub>n</sub>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>  
and (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>, preferably selected from the group  
consisting of alkyl comprising 1 to 4 carbon atoms,  
(CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>k</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>,  
(CH<sub>2</sub>)<sub>n</sub>COOR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup> and especially  
(CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, wherein

n is 0, 1 or 2, preferably 0 or 1;

10 II.11) Ar<sup>1</sup> is phenyl, pyridinyl, oxazolyl, isoxazolyl, pyrazolyl or  
imidazolyl, preferably phenyl, pyridinyl or isoxazolyl and  
especially phenyl or oxazolyl,

p is 1, 2 or 3,

15

R<sup>8</sup> is selected from the group consisting of alkyl comprising  
1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon  
atoms, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, perhaloalkyl comprising  
1 to 4 carbon atoms, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CN, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>,  
20 (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>,  
(CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup> and (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>, wherein

n is 0 or 1,

25

u is 0 or 2, preferably 0, and

q is 0 or 1, and

30

X is selected from the group consisting of O, S, NR<sup>15</sup>,  
CHOR<sup>11</sup>, CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>, OCH<sub>2</sub>, CH<sub>2</sub>O, OCH<sub>2</sub>CH<sub>2</sub>,  
CH<sub>2</sub>CH<sub>2</sub>O, preferably O, S and CH<sub>2</sub> and especially O  
and S,

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- Ar<sup>2</sup> is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 5 R<sup>10</sup> is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, perhaloalkyl comprising 1 to 4 carbon atoms, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CN, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>k</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>, 10 (CH<sub>2</sub>)<sub>n</sub>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup> and (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>, preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>k</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>COOR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup> and especially 15 (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, wherein
- n is 0, 1 or 2, preferably 0 or 1 and
- r is 0, 1 or 2, preferably 0 or 1;
- 20 II.12) p is 1, 2 or 3,
- R<sup>8</sup> is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon 25 atoms, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, perhaloalkyl comprising 1 to 4 carbon atoms, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CN, (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup> and (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>, wherein
- 30 n is 0 or 1,
- u is 0 or 2, preferably 0, and



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- q is 0 or 1, and
- 5 X is selected from the group consisting of O, S,  $\text{NR}^{15}$ ,  $\text{CHOR}^{11}$ ,  $\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2$ ,  $\text{OCH}_2$ ,  $\text{CH}_2\text{O}$ ,  $\text{OCH}_2\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2\text{O}$ , preferably O, S and  $\text{CH}_2$  and especially O and S,
- 10  $\text{Ar}^2$  is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 15  $\text{R}^{10}$  is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH}(\text{Hal})_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$  and  $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$ , preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{13}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$  and especially  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ , wherein
- 20
- 25 n is 0, 1 or 2, preferably 0 or 1 and
- r is 0, 1 or 2, preferably 0 or 1;
- 30 II.13)  $\text{R}^8$  is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH}(\text{Hal})_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,

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$(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  
 $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$  and  $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$ , wherein

- 5                    n            is 0 or 1,
- u            is 0 or 2, preferably 0, and
- q            is 0 or 1, and
- 10                  X            is selected from the group consisting of O, S,  $\text{NR}^{15}$ ,  
 $\text{CHOR}^{11}$ ,  $\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2$ ,  $\text{OCH}_2$ ,  $\text{CH}_2\text{O}$ ,  $\text{OCH}_2\text{CH}_2$ ,  
 $\text{CH}_2\text{CH}_2\text{O}$ , preferably O, S and  $\text{CH}_2$  and especially O  
and S,
- 15                   $\text{Ar}^2$            is phenyl, pyridinyl or pyrimidyl, and especially is phenyl  
or pyridinyl, and
- $\text{R}^{10}$            is selected from the group consisting of H, alkyl  
comprising 1 to 4 carbon atoms, alkoxy comprising 1 to  
20                  4 carbon atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH}(\text{Hal})_2$ , perhaloalkyl  
comprising 1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  
 $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$   
and  $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$ , preferably selected from the group  
25                  consisting of alkyl comprising 1 to 4 carbon atoms,  
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  
 $(\text{CH}_2)_n\text{COOR}^{13}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$  and especially  
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ , wherein
- 30                  n            is 0, 1 or 2, preferably 0 or 1 and
- r            is 0, 1 or 2, preferably 0 or 1;

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- II.14)  $R^8$  is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $CH_2Hal$ ,  $CH(Hal)_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $NO_2$ ,  $(CH_2)_nCN$ ,  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nCOOR^{11}$ ,  $(CH_2)_nCONR^{11}R^{12}$ ,  $(CH_2)_nSO_2NR^{11}R^{12}$  and  $(CH_2)_nS(O)_uR^{13}$ , wherein
- $u$  is 0 or 2, preferably 0, and
- $q$  is 0 or 1, and
- $X$  is selected from the group consisting of O, S,  $NR^{15}$ ,  $CHOR^{11}$ ,  $CH_2$ ,  $CH_2CH_2$ ,  $OCH_2$ ,  $CH_2O$ ,  $OCH_2CH_2$ ,  $CH_2CH_2O$ , preferably O, S and  $CH_2$  and especially O and S,
- $Ar^2$  is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- $R^{10}$  is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $CH_2Hal$ ,  $CH(Hal)_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $NO_2$ ,  $(CH_2)_nCN$ ,  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nCOOR^{11}$ ,  $(CH_2)_nCONR^{11}R^{12}$ ,  $(CH_2)_nSO_2NR^{11}R^{12}$  and  $(CH_2)_nS(O)_uR^{13}$ , preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms,  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nCOOR^{13}$ ,  $(CH_2)_nCONR^{11}R^{12}$  and especially  $(CH_2)_nCONR^{11}R^{12}$ , wherein

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- n is 0, 1 or 2, preferably 0 or 1 and
- r is 0, 1 or 2, preferably 0 or 1;
- 5 II.15)  $R^8$  is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $CH_2Hal$ ,  $CH(Hal)_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $NO_2$ ,  $(CH_2)_nCN$ ,  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nCOOR^{13}$ ,  $(CH_2)_nCONR^{11}R^{12}$ ,  
 10  $(CH_2)_nSO_2NR^{11}R^{12}$  and  $(CH_2)_nS(O)_uR^{13}$ , wherein
- q is 0 or 1, and
- 15 X is selected from the group consisting of O, S,  $NR^{15}$ ,  $CHOR^{11}$ ,  $CH_2$ ,  $CH_2CH_2$ ,  $OCH_2$ ,  $CH_2O$ ,  $OCH_2CH_2$ ,  $CH_2CH_2O$ , preferably O, S and  $CH_2$  and especially O and S,
- 20  $Ar^2$  is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 25  $R^{10}$  is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $CH_2Hal$ ,  $CH(Hal)_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $NO_2$ ,  $(CH_2)_nCN$ ,  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nCOOR^{11}$ ,  $(CH_2)_nCONR^{11}R^{12}$ ,  $(CH_2)_nSO_2NR^{11}R^{12}$  and  $(CH_2)_nS(O)_uR^{13}$ , preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms,  
 30  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nCOOR^{13}$ ,  $(CH_2)_nCONR^{11}R^{12}$  and especially  $(CH_2)_nCONR^{11}R^{12}$ , wherein

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- n is 0, 1 or 2, preferably 0 or 1 and
- r is 0, 1 or 2, preferably 0 or 1;
- 5 II.16) q is 0 or 1, and
- X is selected from the group consisting of O, S,  $\text{NR}^{15}$ ,  $\text{CHOR}^{11}$ ,  $\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2$ ,  $\text{OCH}_2$ ,  $\text{CH}_2\text{O}$ ,  $\text{OCH}_2\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2\text{O}$ , preferably O, S and  $\text{CH}_2$  and especially O and S,
- 10  $\text{Ar}^2$  is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 15  $\text{R}^{10}$  is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH}(\text{Hal})_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$  and  $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$ , preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{13}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$  and especially  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ , wherein
- 20  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{13}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$  and especially  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ , wherein
- 25 n is 0, 1 or 2, preferably 0 or 1 and
- 30 r is 0, 1 or 2, preferably 0 or 1;

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- II.17) X is selected from the group consisting of O, S,  $\text{NR}^{15}$ ,  $\text{CHOR}^{11}$ ,  $\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2$ ,  $\text{OCH}_2$ ,  $\text{CH}_2\text{O}$ ,  $\text{OCH}_2\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2\text{O}$ , preferably O, S and  $\text{CH}_2$  and especially O and S,
- 5  $\text{Ar}^2$  is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 10  $\text{R}^{10}$  is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH}(\text{Hal})_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$  and  $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$ , preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  $(\text{CH}_2)_n\text{COOR}^{13}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$  and especially  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ , wherein
- 15  $n$  is 0, 1 or 2, preferably 0 or 1 and
- 20  $r$  is 0, 1 or 2, preferably 0 or 1;
- 25 II.18)  $\text{Ar}^2$  is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 30  $\text{R}^{10}$  is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH}(\text{Hal})_2$ , perhaloalkyl comprising 1 to 4 carbon atoms,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,

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5 (CH<sub>2</sub>)<sub>n</sub>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>  
and (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>, preferably selected from the group  
consisting of alkyl comprising 1 to 4 carbon atoms,  
(CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>k</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>,  
(CH<sub>2</sub>)<sub>n</sub>COOR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup> and especially  
(CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, wherein

n is 0, 1 or 2, preferably 0 or 1 and

10 r is 0, 1 or 2, preferably 0 or 1;

15 II.19) R<sup>10</sup> is selected from the group consisting of H, alkyl  
comprising 1 to 4 carbon atoms, alkoxy comprising 1 to  
4 carbon atoms, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, perhaloalkyl  
comprising 1 to 4 carbon atoms, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CN,  
(CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>k</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>,  
(CH<sub>2</sub>)<sub>n</sub>COOR<sup>11</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>NR<sup>11</sup>R<sup>12</sup>  
and (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>u</sub>R<sup>13</sup>, preferably selected from the group  
consisting of alkyl comprising 1 to 4 carbon atoms,  
20 (CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>k</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>,  
(CH<sub>2</sub>)<sub>n</sub>COOR<sup>13</sup>, (CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup> and especially  
(CH<sub>2</sub>)<sub>n</sub>CONR<sup>11</sup>R<sup>12</sup>, wherein

25 n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

30 II.20) R<sup>10</sup> is selected from the group consisting of H, alkyl  
comprising 1 to 4 carbon atoms, alkoxy comprising 1 to  
4 carbon atoms, Hal, CH<sub>2</sub>Hal, CH(Hal)<sub>2</sub>, perhaloalkyl  
comprising 1 to 4 carbon atoms, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>n</sub>CN,  
(CH<sub>2</sub>)<sub>n</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>k</sub>NR<sup>11</sup>R<sup>12</sup>, (CH<sub>2</sub>)<sub>n</sub>COR<sup>13</sup>,

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$(\text{CH}_2)_n\text{COOR}^{11}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$   
 and  $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$ , preferably selected from the group  
 consisting of alkyl comprising 1 to 4 carbon atoms,  
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$ ,  $(\text{CH}_2)_n\text{COR}^{13}$ ,  
 5  $(\text{CH}_2)_n\text{COOR}^{13}$ ,  $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$  and especially  
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ , and

$r$  is 0, 1 or 2, preferably 0 or 1.

10 One preferred embodiment of the instant invention relates to compounds  
 of formula II and preferably one or more of sub formulae II.1) to II.20),  
 wherein  $p$  is 1, 2 or 3 and  $\text{R}^8$  is independently selected from the group  
 consisting of methyl, ethyl, isopropyl, tert.-butyl, F, Cl, Br,  $\text{CF}_3$ ,  $\text{C}(\text{CF}_3)_3$ ,  
 methoxy, ethoxy, tert.-butoxy, perfluoro tert.-butoxy ( $\text{OC}(\text{CF}_3)_3$ ), methyl  
 15 sulfanyl ( $\text{SCH}_3$ ), ethyl sulfanyl ( $\text{SCH}_2\text{CH}_3$ ), acetyl ( $\text{COCH}_3$ ), propionyl  
 ( $\text{COCH}_2\text{CH}_3$ ), butyryl ( $\text{COCH}_2\text{CH}_2\text{CH}_3$ ). If  $p$  is 2 or 3, all substituents can  
 be the same or different.

20 Another preferred embodiment of the instant invention relates to  
 compounds of formula II and preferably one or more of sub formulae II.1)  
 to II.20), wherein  $X$  is selected from the group consisting of S,  $\text{N-R}^{21}$ ,  $\text{CH}_2$ ,  
 $\text{CH}_2\text{CH}_2$ ,  $\text{OCH}_2$  and  $\text{CH}_2\text{O}$ .

25 Another preferred embodiment of the instant invention relates to  
 compounds of formula II and preferably one or more of sub formulae II.1)  
 to II.20), wherein  $X$  is selected from the group consisting of S,  $\text{CH}_2$ .

30 Another even more preferred embodiment of the instant invention relates  
 to compounds of formula II and preferably one or more of sub formulae  
 II.1) to II.20), wherein  $X$  is O.



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Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Y is selected from the group consisting of  $C(R^{22})-NO_2$ ,  $C(R^{22})-CN$  and  $C(CN)_2$ .

5

Another more preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Y is selected from the group consisting of O, S and  $NR^{21}$ .

10 Another even more preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Y is selected from the group consisting of O and S.

15 Another even more preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein Y is O.

20 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $Ar^2$  is pyridinyl.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein r is either 0 or 1. If r is 1,  $R^{10}$  is preferably  
25  $(CH_2)_nCONR^{11}R^{12}$  and especially  $(CH_2)_nCONR^{11}R^{12}$ , wherein n is 0. In this embodiment,  $R^{11}$  is preferably selected from the group consisting of H and A and more preferred from H and alkyl, and  $R^{12}$  is preferably selected from the group consisting of H and A and more preferred from H and alkyl.  
Especially preferred as residue  $R^{10}$  are carbamoyl, more preferred alkyl  
30 carbamoyl or diaalkyl carbamoyl, even more preferred methyl carbamoyl or dimethyl carbamoyl, ethyl carbamoyl or diethyl carbamoyl and especially preferred methyl carbamoyl ( $-CONHCH_3$ ). This embodiment is especially

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preferred when  $Ar^2$  is pyridinyl. When  $Ar^2$  is pyridinyl,  $R^{10}$  is preferably bonded in a vicinal position to the nitrogen atom of the pyridinyl residue, i.e. in 2- and/or 6-position of the pyridinyl residue.

- 5 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $r$  is either 0 or 1. If  $r$  is 1,  $R^{10}$  is preferably  $(CH_2)_nCONR^{11}R^{12}$  and especially  $(CH_2)_nCONR^{11}R^{12}$ , wherein  $n$  is 0. In this embodiment,  $R^{11}$  is preferably selected from the group consisting of H and
- 10 A, more preferred from H and alkyl and especially is H, and  $R^{12}$  is preferably selected from the group consisting of H and A and more preferred from H, unsubstituted alkyl and substituted alkyl, preferably comprising 1 to 6 and especially 1 or 2 carbon atoms. Suitable for substituents include amino groups, such as  $NH_2$ ,  $NHCH_3$ ,  $NHCH_2CH_3$ ,
- 15  $N(CH_3)_2$  and  $NH(CH_2CH_3)$ , and carboxyl groups and derivatives thereof, such as  $COOH$ ,  $COOCH_3$ ,  $CONH_2$ , and  $CONHCH_3$ . Especially preferred as residue  $R^{10}$  are  $CONHCH_3$ ,  $CONHCH_2CH_2NH_2$ ,  $CONHCH_2CH_2NHCH_3$ ,  $CONHCH_2CH_2N(CH_3)_2$ ,  $CONHCH_2COOH$  and  $CONHCH_2CH_2COOH$ . This embodiment is especially preferred when  $Ar^2$  is pyridinyl. When  $Ar^2$  is
- 20 pyridinyl,  $R^{10}$  is preferably bonded in a vicinal position to the nitrogen atom of the pyridinyl residue, i.e. in 2- and/or 6-position of the pyridinyl residue.

- Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $Ar^1$  comprises two or more substituents  $R^8$ , wherein one
- 25 or more, preferably one substituent  $R^8$  is selected from the group consisting of  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$ ,  $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$ ,  $(CH_2)_nCOOR^{11}$  and  $(CH_2)_nS(O)_uR^{13}$  wherein  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are defined as above and  $n$  is as
- 30 defined above, preferably  $n$  is 0, 1 or 2 and especially is 0,  $k$  is 1 to 4 and preferably 1 or 2, and  $u$  is preferably 2. In this embodiment  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are more preferably selected independently from each other from the

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group consisting of H, methyl and ethyl. In this embodiment, one or two substituents  $R^8$  and preferably one substituent  $R^8$  is especially preferably selected from the group consisting of  $NH_2$ ,  $N(CH_3)_2$ ,  $N(C_2H_5)_2$ ,  $NHCH_2CH_2NH_2$ ,  $N(CH_3)CH_2CH_2NH_2$ ,  $N(CH_3)CH_2CH_2N(CH_3)_2$ ,  
 5  $N(CH_3)CH_2CH_2N(CH_3)_2$ ,  $N(CH_3)CH_2CH_2OCH_3$ ,  $OCH_2CH_2N(CH_3)_2$ ,  $SCH_3$ ,  $SC_2H_5$ ,  $SO_2CH_3$ ,  $COOCH_3$  and  $COOH$ . Accordingly, in this embodiment  $Ar^1$  especially preferably comprises at least one substituent  $R^8$  other than  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$ ,  $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$ ,  $(CH_2)_nCOOR^{13}$  and  $(CH_2)_nS(O)_uR^{13}$  as defined  
 10 in this paragraph and especially other than  $NH_2$ ,  $N(CH_3)_2$ ,  $N(C_2H_5)_2$ ,  $NHCH_2CH_2NH_2$ ,  $N(CH_3)CH_2CH_2NH_2$ ,  $N(CH_3)CH_2CH_2N(CH_3)_2$ ,  $N(CH_3)CH_2CH_2N(CH_3)_2$ ,  $N(CH_3)CH_2CH_2OCH_3$ ,  $OCH_2CH_2N(CH_3)_2$ ,  $SCH_3$ ,  $SC_2H_5$ ,  $SO_2CH_3$ ,  $COOCH_3$  and  $COOH$ .

15 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $q$  is 1, i.e. the phenylen moiety bound to the glycine amide group and the radical  $X$  is substituted once, preferably by a substituent selected from the group consisting of alkyl and halogen and  
 20 more preferred from methyl, ethyl, F, Cl and Br.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $q$  is 0, i.e. the phenylen moiety bound to the glycine  
 25 amide group and the radical  $X$  is unsubstituted.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of formulae II.1) to II.20), wherein  $(R^8)_p-Ar^1$  is selected from the group consisting of 3-acetyl-phenyl, 4-acetyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 4-bromo-2-chloro-phenyl, 4-bromo-3-methyl-phenyl, 4-bromo-3-trifluoromethyl-phenyl, 2-chloro-phenyl, 2-chloro-4-trifluoromethyl-phenyl,  
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2-chloro-5-trifluoromethyl-phenyl, 3-chloro-phenyl, 3-chloro-4-methyl-phenyl, 3-chloro-4-methoxy-phenyl, 3-chloro-4-methoxy-phenyl, 4-chloro-phenyl, 4-chloro-2-trifluoromethyl-phenyl, 4-chloro-3-trifluoromethyl-phenyl, 4-chloro-2-methyl-phenyl, 5-chloro-2-methyl-phenyl, 5-chloro-2-methoxy-phenyl, 4-chloro-2-methoxy-5-methyl-phenyl, 4-chloro-2-methoxy-5-trifluoromethyl-phenyl, 2,3-dichloro-phenyl, 2,4-dichloro-phenyl, 2,5-dichloro-phenyl, 3,4-dichloro-phenyl, 3,5-dichloro-phenyl, 2,4,5-trichloro-phenyl, 4-fluoro-phenyl, 4-fluoro-3-trifluoromethyl-phenyl, 4-ethoxy-phenyl, 2-methoxy-phenyl, 2-methoxy-5-trifluoromethyl-phenyl, 4-methoxy-phenyl, 2,5-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethyl-phenyl, 4-trifluoromethoxy-phenyl, 3,5-bis-trifluoromethyl-phenyl, 3-methoxy-phenyl, 3-methylsulfanyl-phenyl, 4-methylsulfanyl-phenyl, o-tolyl (2-methyl-phenyl), m-tolyl (3-methyl-phenyl), p-tolyl (4-methyl-phenyl), 2,3-dimethyl-phenyl, 2,3-dimethyl-phenyl, 2,5-dimethyl-phenyl, 3,4-dimethyl-phenyl, 3,5-dimethyl-phenyl, 2-ethyl-phenyl, 3-ethyl-phenyl, 4-ethyl-phenyl, 4-isopropyl-phenyl, 4-tert-butyl-phenyl and 5-tert-butyl-isoxazol-3-yl.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $(R^8)_p-Ar^1$  is as defined above, but comprises one or more additional residues, preferably one additional residue. The additional residues are preferably selected from the meanings given for  $R^8$  and more preferably selected from the group consisting of  $(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$ ,  $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$ ,  $(CH_2)_nCOOR^{13}$  and  $(CH_2)_nS(O)_uR^{13}$  wherein  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. In this embodiment  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. Even more preferred, the additional residue(s) is/are selected from the group consisting of  $NH_2$ ,  $N(CH_3)_2$ ,  $N(C_2H_5)_2$ ,  $NHCH_2CH_2NH_2$ ,  $N(CH_3)CH_2CH_2NH_2$ ,

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$N(CH_3)CH_2CH_2N(CH_3)_2$ ,  $N(CH_3)CH_2CH_2N(CH_3)_2$ ,  $N(CH_3)CH_2CH_2OCH_3$ ,  $OCH_2CH_2N(CH_3)_2$ ,  $SC_2H_5$ ,  $SO_2CH_3$ ,  $COOCH_3$  and  $COOH$ .

5 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein X is bonded in the para- (p-) or metha- (m-)position to the phenyl residue that is bonded directly to the glycine amide moiety.

10 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $Ar^2$  is a pyridinyl residue and wherein said pyridinyl residue is bonded to X in the 3- or 4-position, preferably the 4-position, relative to the nitrogen atom of the pyridinyl residue.

15 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $Ar^2$  comprises one or more substituents  $R^{10}$  and wherein one or two, preferably one substituent  $R^{10}$  is selected from unsubstituted or substituted carbamoyl moieties. Substituted carbamoyl moieties are  
20 preferably selected from  $CONHR^{23}$  or  $CONR^{23}R^{24}$ , preferably  $CONHR^{23}$ , wherein  $R^{23}$  and  $R^{24}$  are independently selected from the definitions given for  $R^8$ , more preferably selected from alkyl, preferably methyl, ethyl, propyl and butyl,  $(CH_2)_nNR^{11}R^{12}$  and  $(CH_2)_nOR^{12}$ , wherein  $R^{11}$ ,  $R^{12}$  and n are as defined above. In this embodiment, n is preferably not 0 and more  
25 preferred 1 to 3 and especially 1 or 2. Preferred examples for  $R^{23}$  are selected from the group consisting of methyl, ethyl,  $CH_2CH_2NH_2$ ,  $CH_2CH_2N(CH_3)_2$ ,  $CH_2CH_2N(CH_2CH_3)_2$ ,  $CH_2CH_2OH$ ,  $CH_2CH_2OCH_3$  and  $CH_2CH_2OCH_2CH_3$ .

30 Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $Ar^2$  comprises one or more substituents  $R^{10}$  and wherein

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one or two, preferably one substituent  $R^{10}$  is selected from substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from  $CONHR^{23}$ , wherein  $R^{23}$  is preferably unsubstituted  $C_1$ - $C_4$ -alkyl and especially methyl.

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Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $Ar^2$  comprises one or more substituents  $R^{10}$  and wherein one or two, preferably one substituent  $R^{10}$  is selected from substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from  $CONHR^{23}$ , wherein  $R^{23}$  is selected from  $(CH_2)_nNR^{11}R^{12}$  and  $(CH_2)_nOR^{12}$ , wherein  $R^{11}$ ,  $R^{12}$  and  $n$  are as defined above. In this embodiment,  $n$  is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for  $R^{23}$  are selected from the group consisting of  $CH_2CH_2NH_2$ ,  $CH_2CH_2N(CH_3)_2$ ,  $CH_2CH_2N(CH_2CH_3)_2$ ,  $CH_2CH_2OH$ ,  $CH_2CH_2OCH_3$  and  $CH_2CH_2OCH_2CH_3$ .

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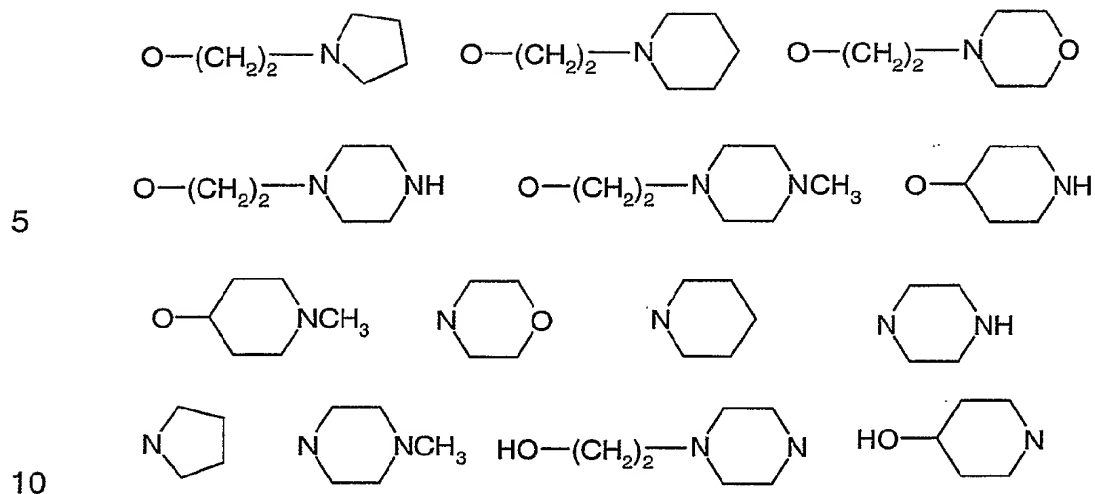
Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $Ar^1$  comprises one or more substituents  $R^8$  and wherein one or two, preferably one substituent  $R^8$  is selected from the group consisting of  $NH_2$ ,  $N(CH_3)_2$ ,  $NHCH_3$ ,  $N(C_2H_5)_2$ ,  $HNCH_2CH_2NH_2$ ,  $OCH_2CH_2NH_2$ ,  $HOCH_2CH_2NH$ ,  $OCH_2CH_2NHCH_3$ ,  $N(CH_3)CH_2CH_2NH_2$ ,  $HN(CH_3)CH_2CH_2NH$ ,  $N(CH_3)CH_2CH_2N(CH_3)_2$ ,  $N(CH_3)CH_2CH_2N(CH_3)_2$ ,  $N(CH_3)CH_2CH_2OCH_3$ ,  $OCH_2CH_2N(CH_3)_2$ ,  $OCH_2CH_2N(CH_2CH_3)_2$ ,  $SCH_3$ ,  $SC_2H_5$ , and compounds of the formulae

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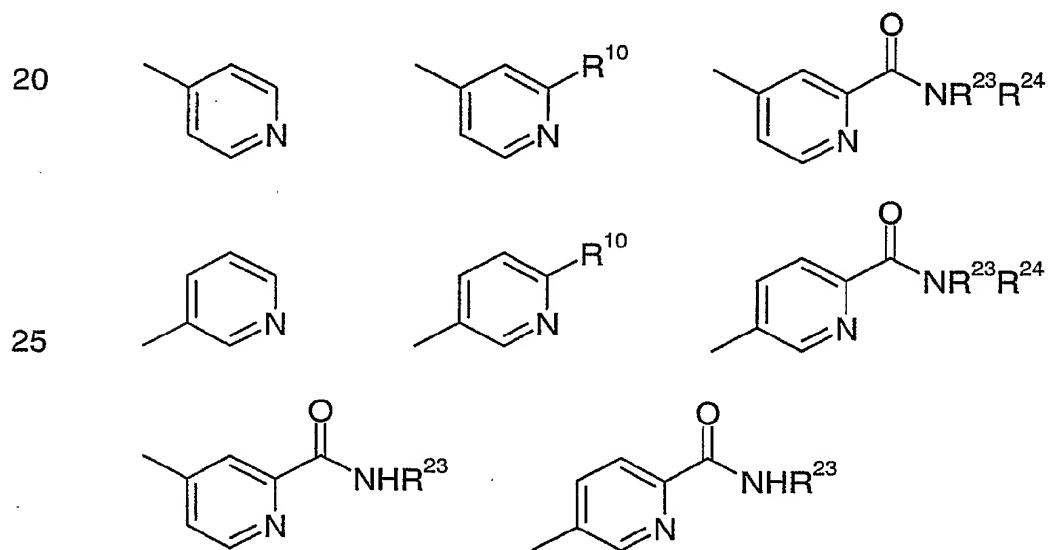
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and/or  $\text{Ar}^2$  comprises one or more substituents  $\text{R}^{10}$  and wherein one or two, preferably one substituent  $\text{R}^{10}$  is independently selected from the meanings given for  $\text{R}^8$  in this paragraph.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein  $-\text{Ar}^2-(\text{R}^{10})_r$  is selected from the formulae



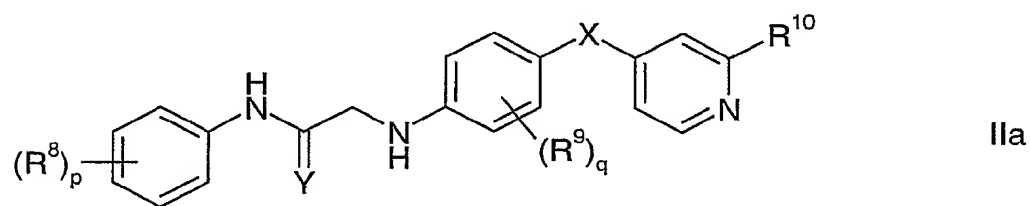
wherein  $\text{R}^{10}$ ,  $\text{R}^{23}$  and  $\text{R}^{24}$  are as defined above and below.

Another especially preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20), wherein one or more features of the above and below mentioned embodiments are combined in one compound.

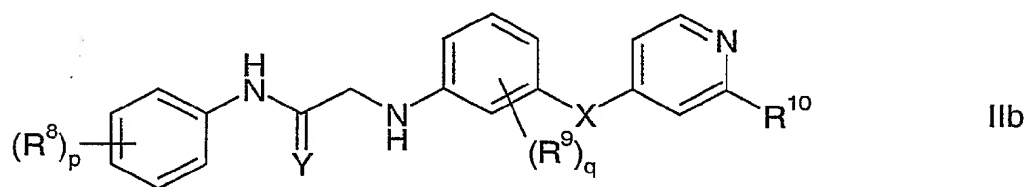
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Subject of the present invention are therefore especially preferred compounds of formula II according to one or more of the formulae IIa, IIb, IIc, IId, IIe, IIf, IIg and IIh,

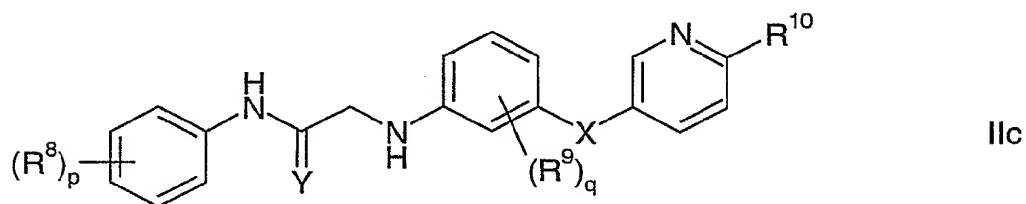
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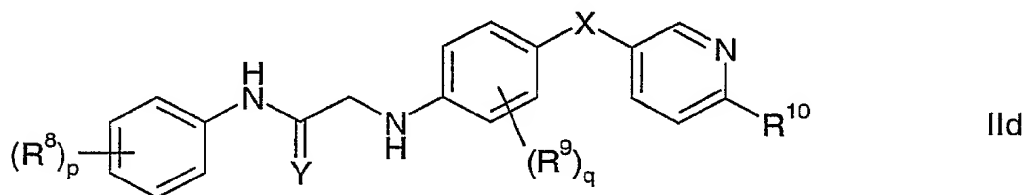
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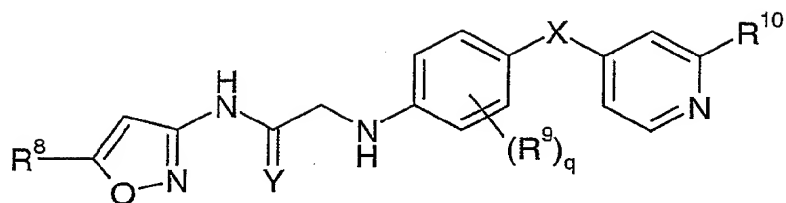
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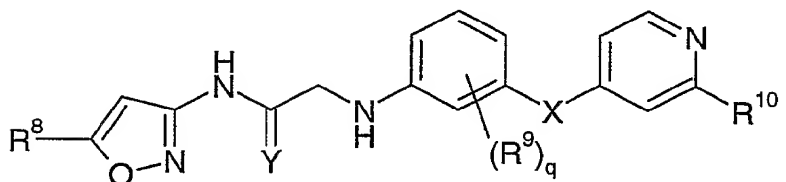


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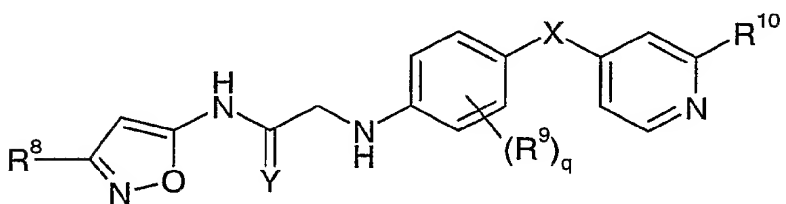
IIe

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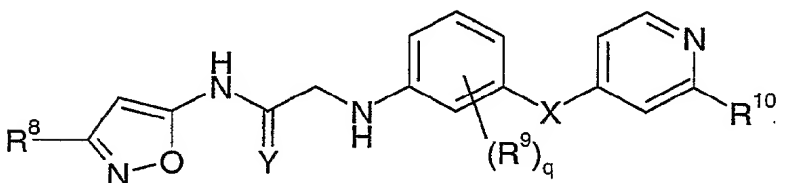
IIlf

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IIlg

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IIlh

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wherein  $R^8$ ,  $p$ ,  $Y$ ,  $R^9$  and  $q$  are as defined above and below,  $R^{10}$  is H or as defined above/below, and preferably as defined in sub formulae II.1) to II.20) and/or the embodiments related thereto.

Another preferred embodiment of the instant invention relates to compounds of formula II and preferably one or more of sub formulae II.1) to II.20) and IIa to IIh, wherein  $R^{10}$  is H or a substituted carbamoyl moiety  $\text{CONHR}^{23}$  or  $\text{CONR}^{23}\text{R}^{24}$ , preferably  $\text{CONHR}^{23}$ , wherein  $R^{23}$  and  $R^{24}$  are independently selected from the definitions given for  $R^8$ , more preferably selected from  $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$  and  $(\text{CH}_2)_n\text{OR}^{12}$ , wherein  $R^{11}$ ,  $R^{12}$  and  $n$  are as defined above. In this embodiment,  $n$  is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for  $R^{23}$  are

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selected from the group consisting of  $\text{CH}_2\text{CH}_2\text{NH}_2$ ,  $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ ,  $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$ ,  $\text{CH}_2\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{CH}_2\text{OCH}_3$  and  $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ .

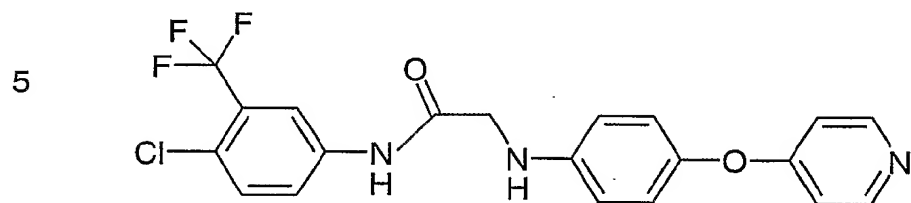
It is understood that when a residue, for example  $\text{R}^8$ ,  $\text{R}^9$ ,  $\text{R}^{10}$  or  $\text{R}^{14}$  or  $\text{R}^{23}$ ,  
 5 is comprised twice or more times in one or more of the formulae I, II and the sub formulae corresponding thereto, it is in each case independently from one another selected from the meanings given for the respective residue. For example,  $\text{R}^{11}$  and  $\text{R}^{12}$  are defined to be independently selected from a group consisting of H, A,  $(\text{CH}_2)_m\text{Ar}^3$  and  $(\text{CH}_2)_m\text{Het}$ . Then  
 10  $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_m\text{NR}^{12}\text{R}^{12}$  can be  $(\text{CH}_2)_n\text{NA}(\text{CH}_2)_m\text{NA}_2$  (if  $\text{R}^{11} = \text{A}$ ,  $\text{R}^{12} = \text{A}$  and  $\text{R}^{12} = \text{H}$ ) as well as  $(\text{CH}_2)_n\text{NA}(\text{CH}_2)_m\text{NHA}$  (if  $\text{R}^{11} = \text{A}$ ,  $\text{R}^{12} = \text{H}$  and  $\text{R}^{12} = \text{A}$  or  $(\text{CH}_2)_n\text{NA}(\text{CH}_2)_m\text{NH}(\text{CH}_2)_m\text{Het}$  (if  $\text{R}^{11} = \text{A}$ ,  $\text{R}^{12} = \text{H}$  and  $\text{R}^{12} = (\text{CH}_2)_m\text{Het}$ ). Accordingly, if a compound of formula II comprises one residue  $\text{R}^8\text{H}$ ,  $\text{R}^9\text{H}$  and  $\text{R}^{10}$ , then for example  $\text{R}^8$ ,  $\text{R}^9$  and  $\text{R}^{10}$  can all be  
 15  $(\text{CH}_2)_n\text{COOR}^{13}$ , wherein all residues  $\text{R}^{13}$  are the same (for example  $\text{CH}_2\text{Hal}$ , wherein Hal is Cl; then all residues  $\text{R}^8$ ,  $\text{R}^9$  and  $\text{R}^{10}$  are the same) or different (for example  $\text{CH}_2\text{Hal}$ , wherein in  $\text{R}^8$  Hal is cl; in  $\text{R}^9$  Hal is F; and in  $\text{R}^{10}$  Hal is Br; then all residues  $\text{R}^8$ ,  $\text{R}^9$  and  $\text{R}^{10}$  are different); or for example  $\text{R}^8$  is  $(\text{CH}_2)_n\text{COOR}^{13}$ ,  $\text{R}^9$  is  $\text{NO}_2$  and  $\text{R}^{10}$  is  $(\text{CH}_2)_n\text{SR}^{11}$ , wherein  
 20  $\text{R}^{11}$  and  $\text{R}^{13}$  can be the same (for example both can be H or both can be A which is methyl) of different (for example  $\text{R}^{11}$  can be H and  $\text{R}^{13}$  can be A which is methyl).

If not stated otherwise, reference to compounds of formula I and formula II  
 25 also includes the sub formulae related thereto, especially sub formulae II.1) to II.20) and IIa to IIh.

Subject of the instant invention are especially those compounds of formula I and/or formula II, in which at least one of the residues mentioned in said  
 30 formulae has one of the preferred or especially preferred meanings given above and below.

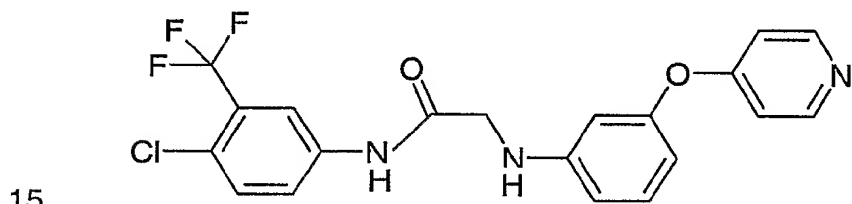
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The present invention further relates to compounds (1) to (8) as given below:

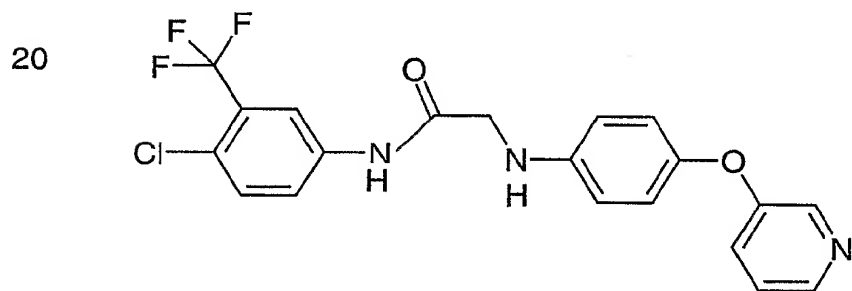


(1): N-(4-Chloro-3-trifluoromethyl-phenyl)-2-[4-(pyridin-4-yloxy)-phenylamino]-acetamide

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(2): N-(4-Chloro-3-trifluoromethyl-phenyl)-2-[3-(pyridin-4-yloxy)-phenylamino]-acetamide



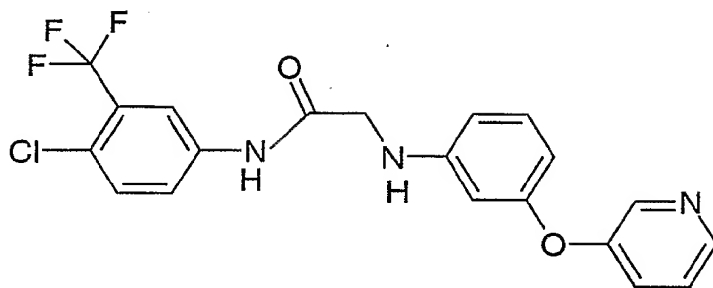
(3): N-(4-Chloro-3-trifluoromethyl-phenyl)-2-[4-(pyridin-3-yloxy)-phenylamino]-acetamide

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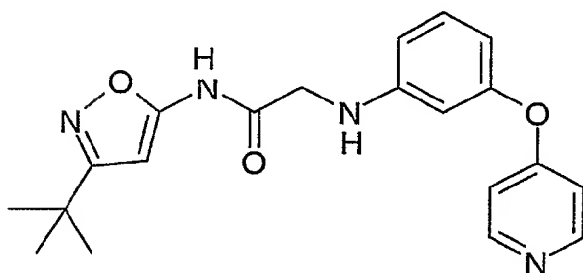
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(4): N-(4-Chloro-3-trifluoromethyl-phenyl)-2-[3-(pyridin-3-yloxy)-phenylamino]-acetamide

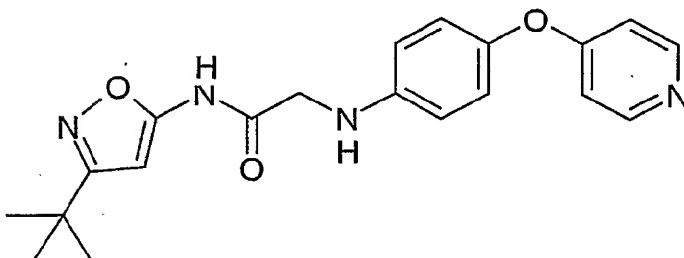
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(5): N-(3-tert.-Butyl-isoxazol-5-yl)-2-[3-(pyridin-4-yloxy)-phenylamino]-acetamide

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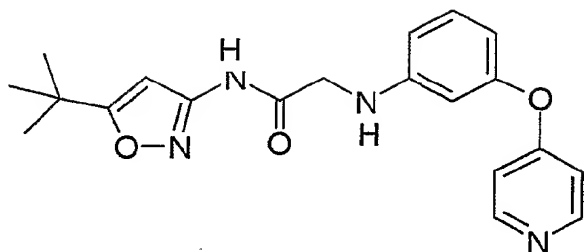
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(6): N-(3-tert.-Butyl-isoxazol-5-yl)-2-[4-(pyridin-4-yloxy)-phenylamino]-acetamide

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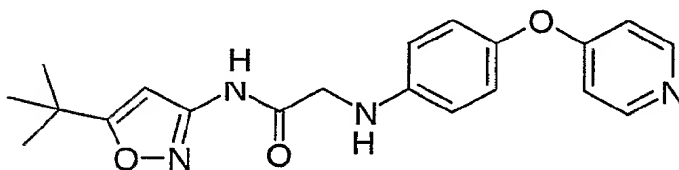
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(7): N-(5-tert.-Butyl-isoxazol-3-yl)-2-[3-(pyridin-4-yloxy)-phenylamino]-acetamide

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(8): N-(5-tert.-Butyl-isoxazol-3-yl)-2-[4-(pyridin-4-yloxy)-phenylamino]-acetamide

The present invention also relates to compounds (9) to (235) of formula  
A-NH-CO-CH<sub>2</sub>-NH-B, wherein A and B are as given in the table  
below:

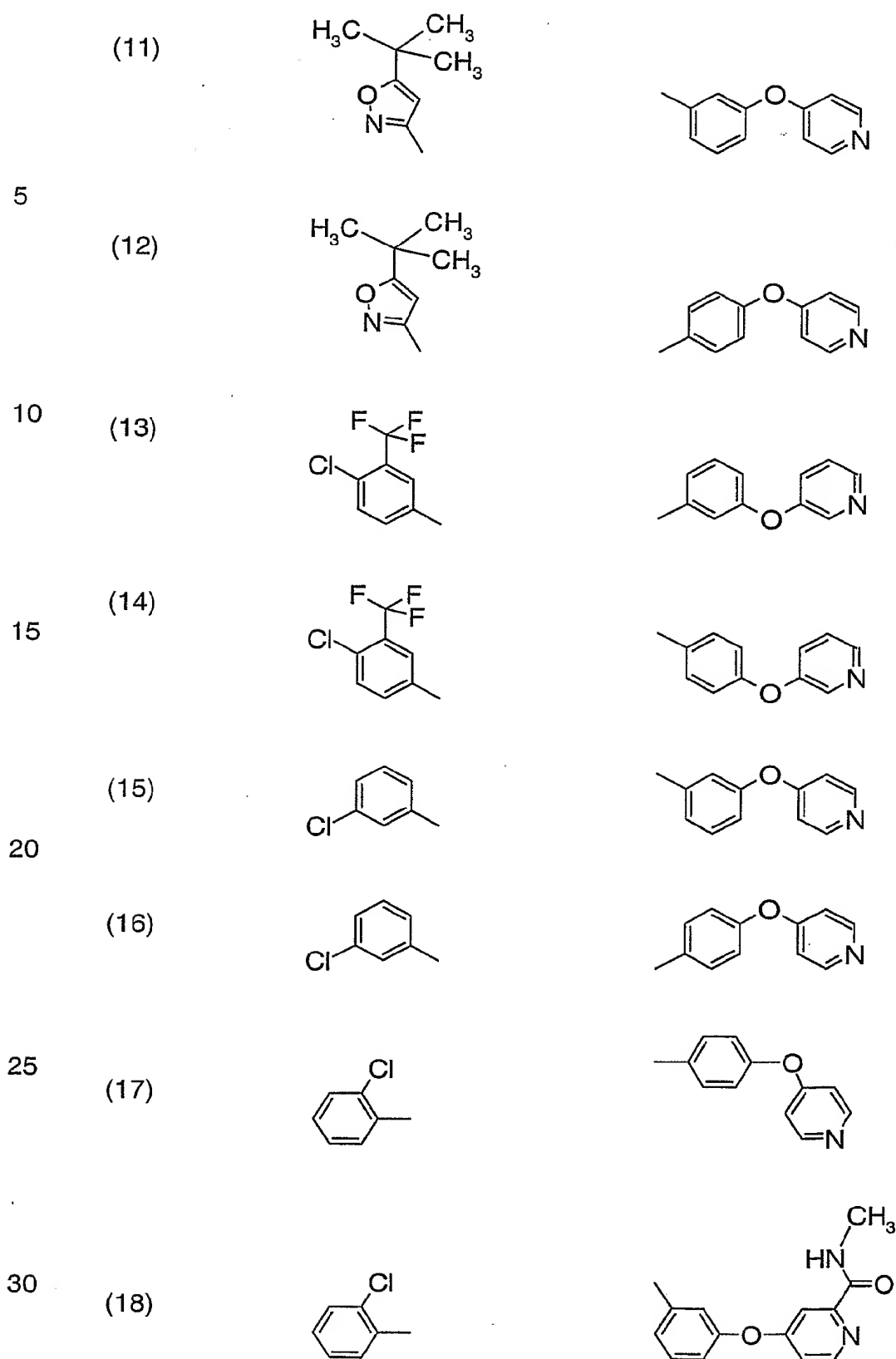
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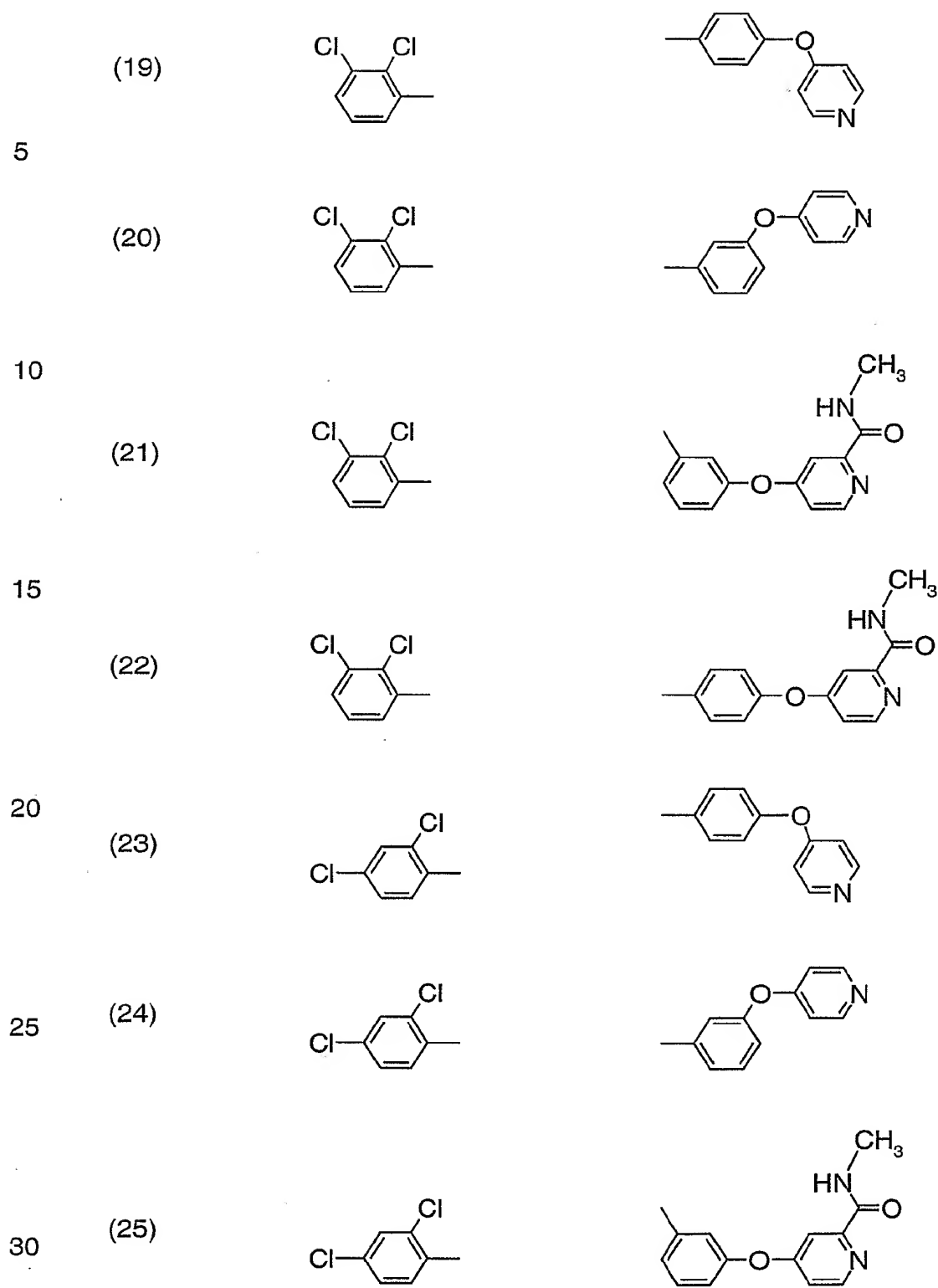
	A	B
(9)		
(10)		

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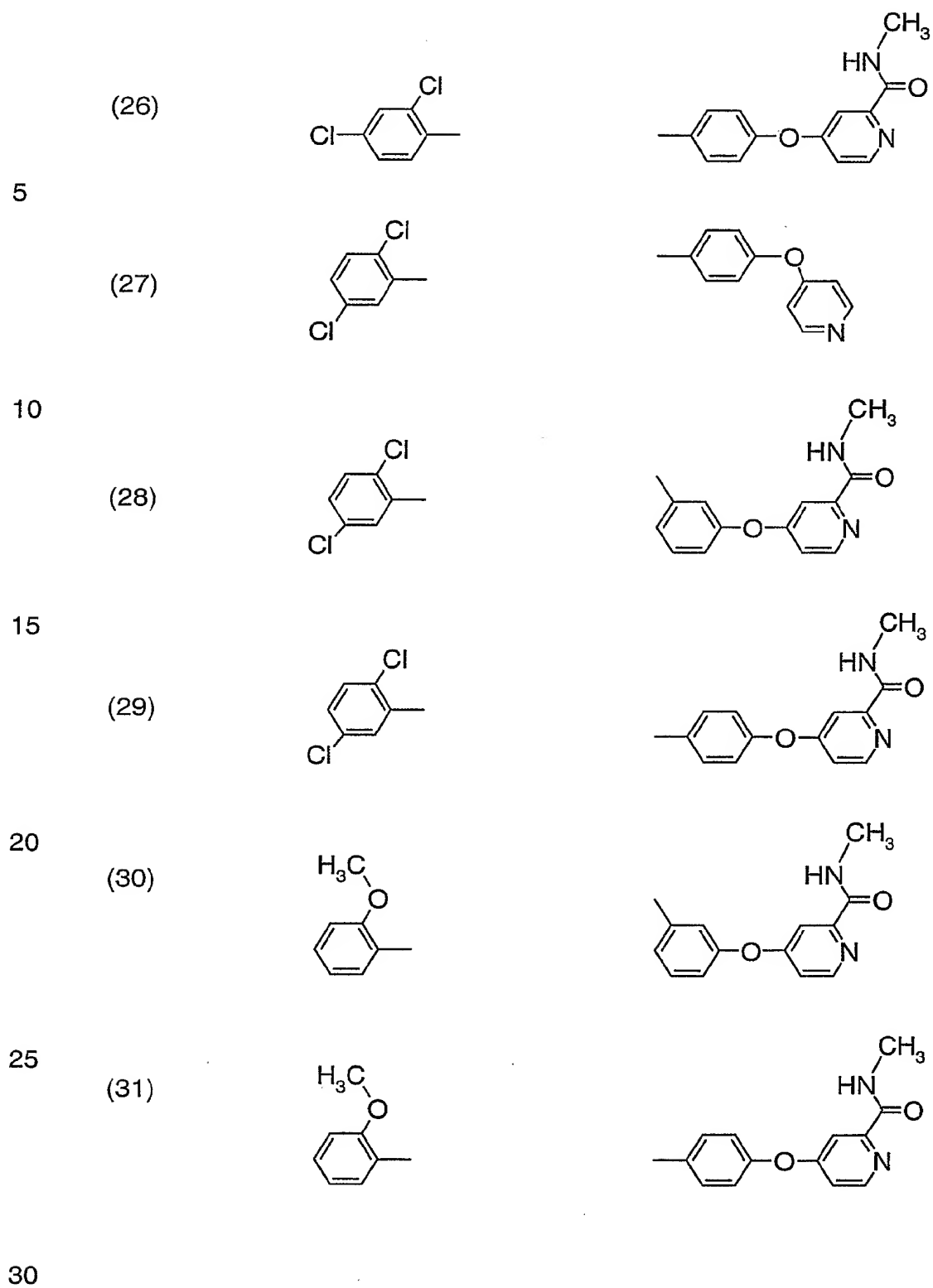
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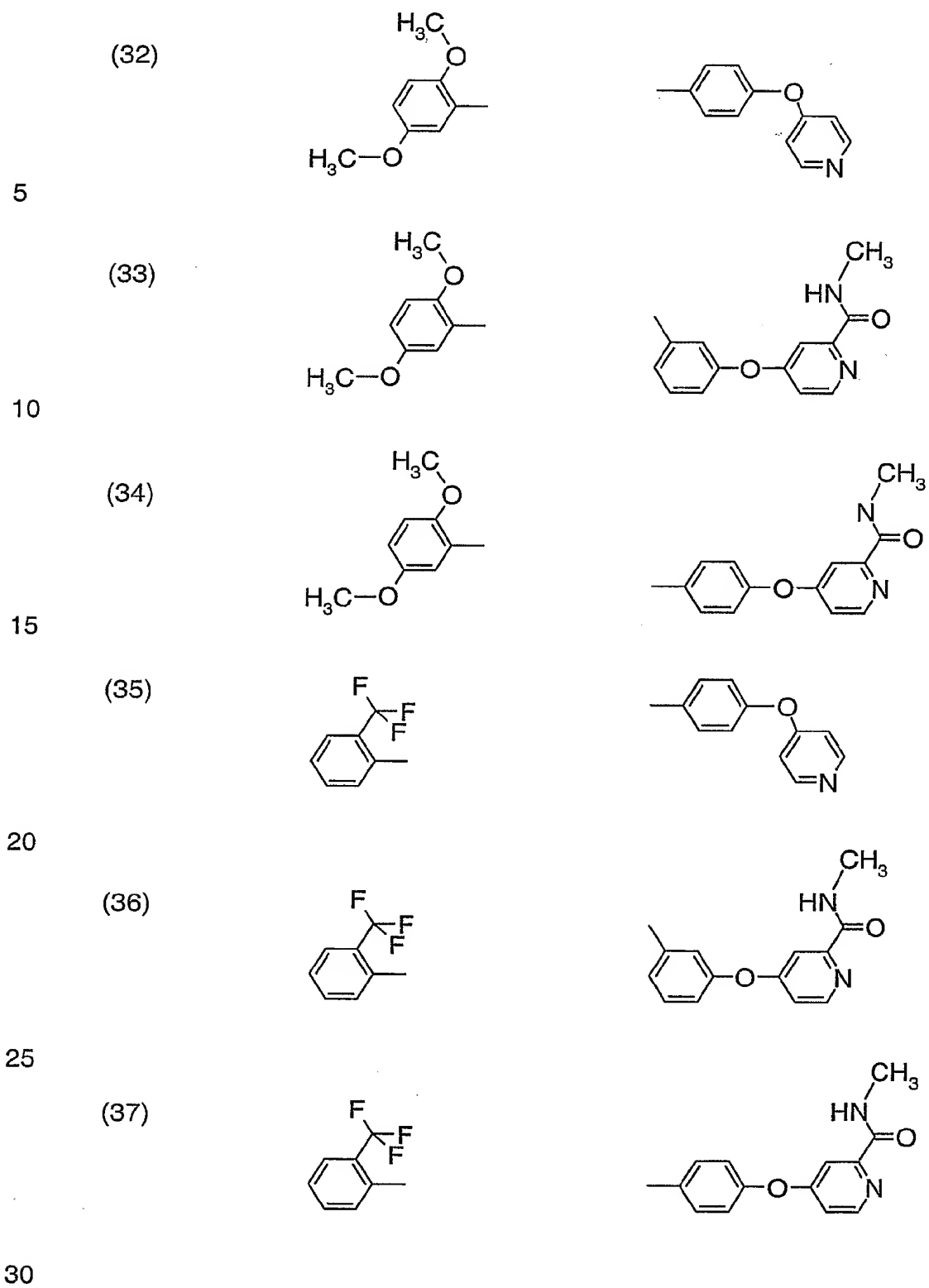


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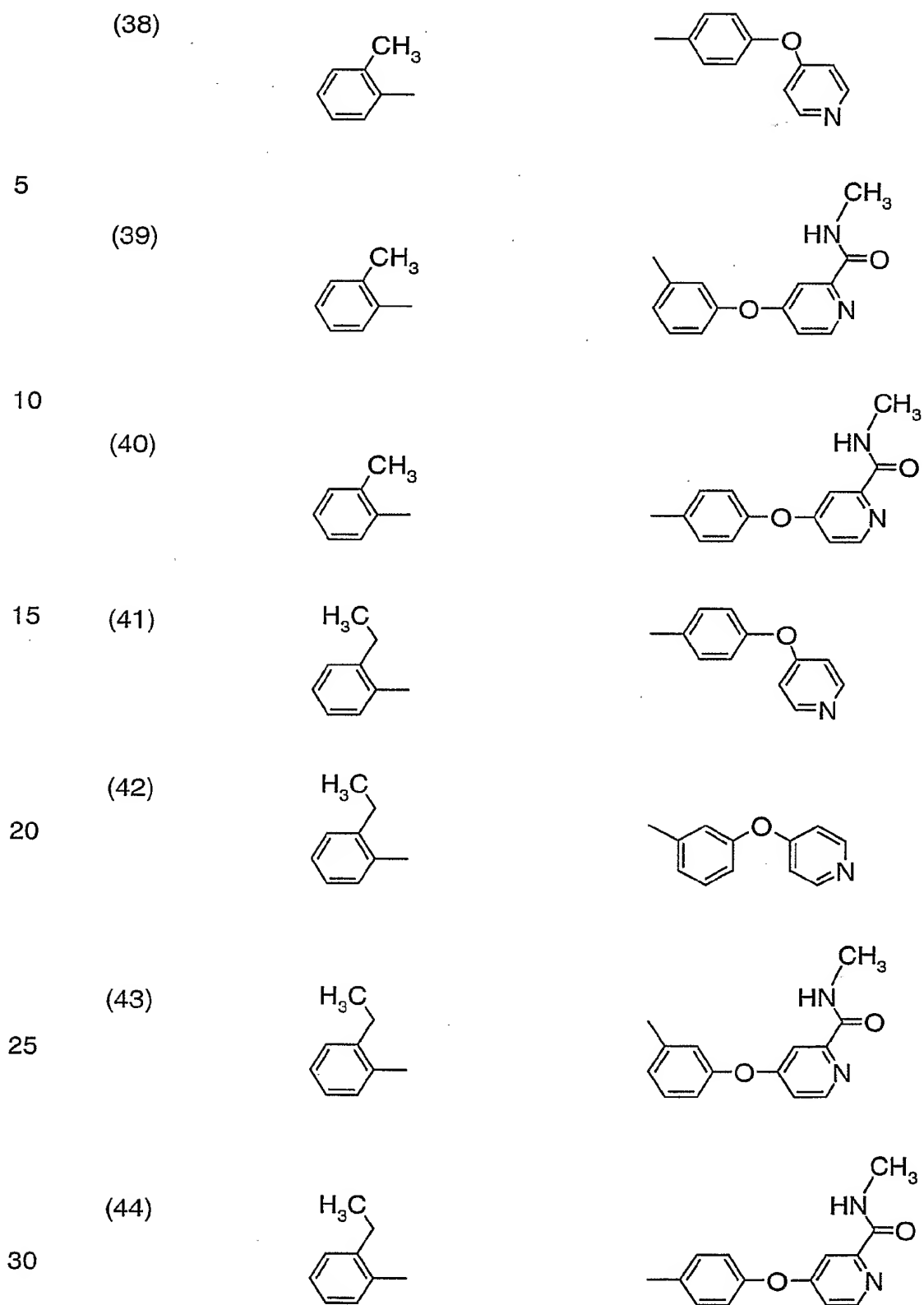




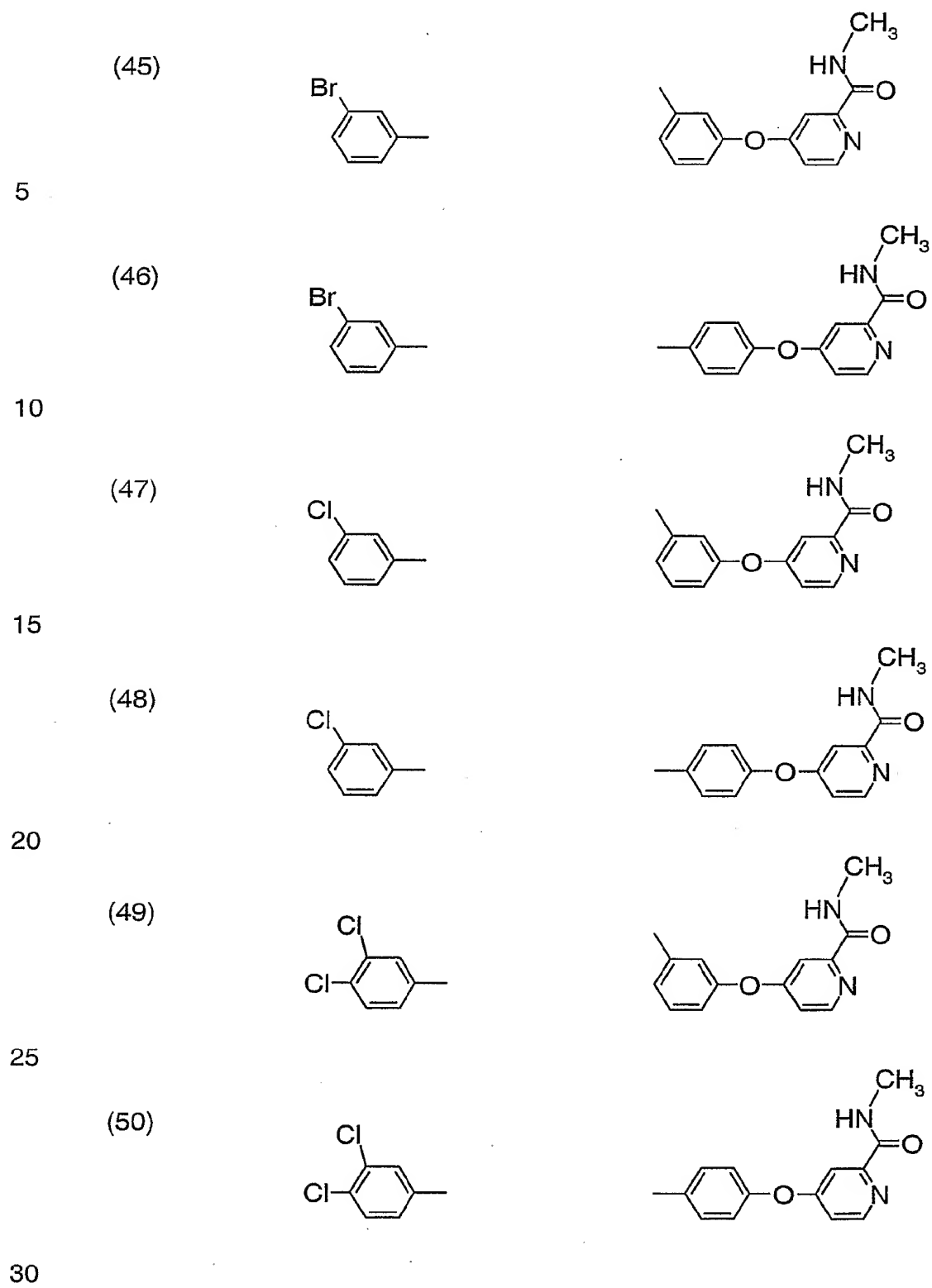
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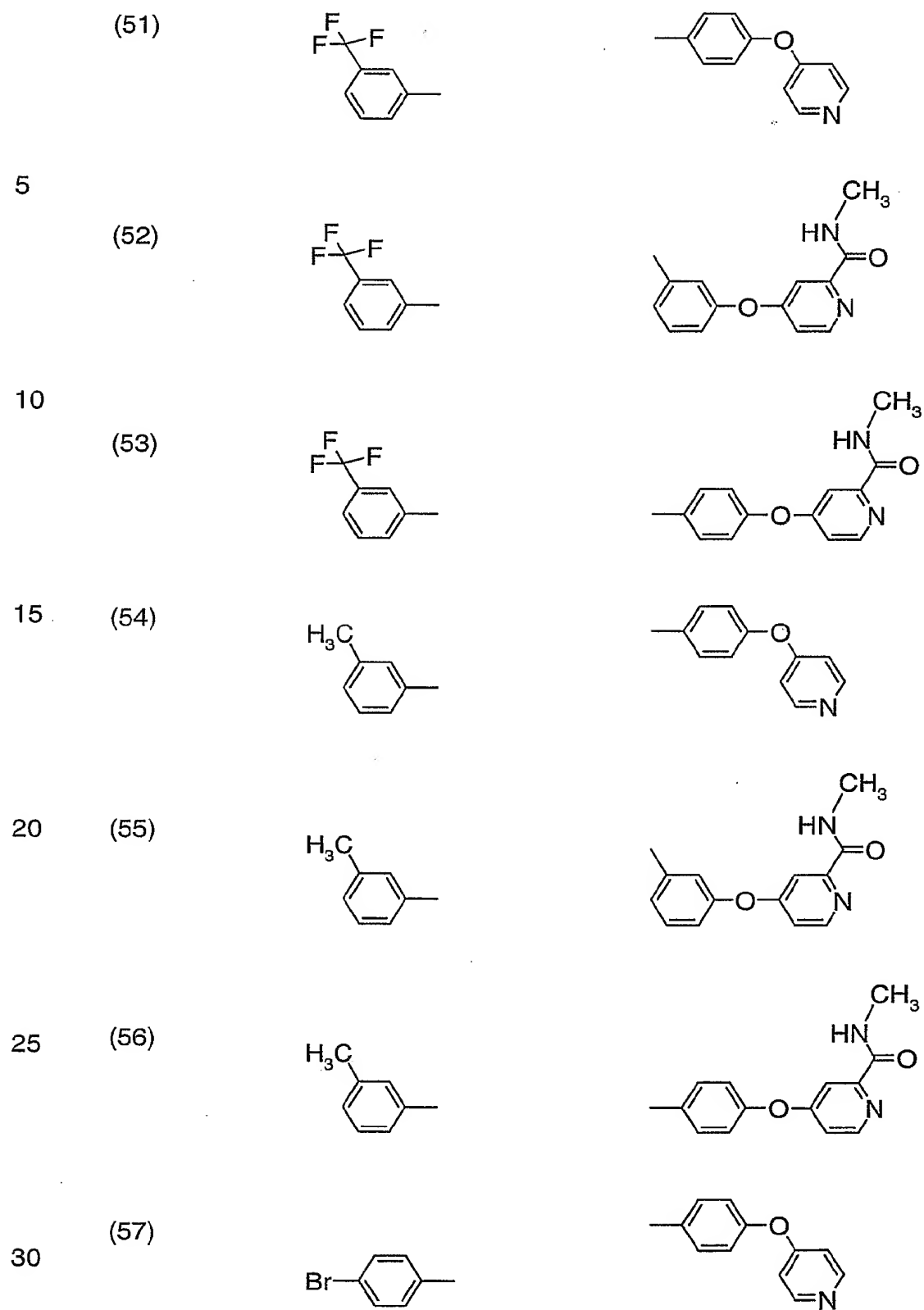
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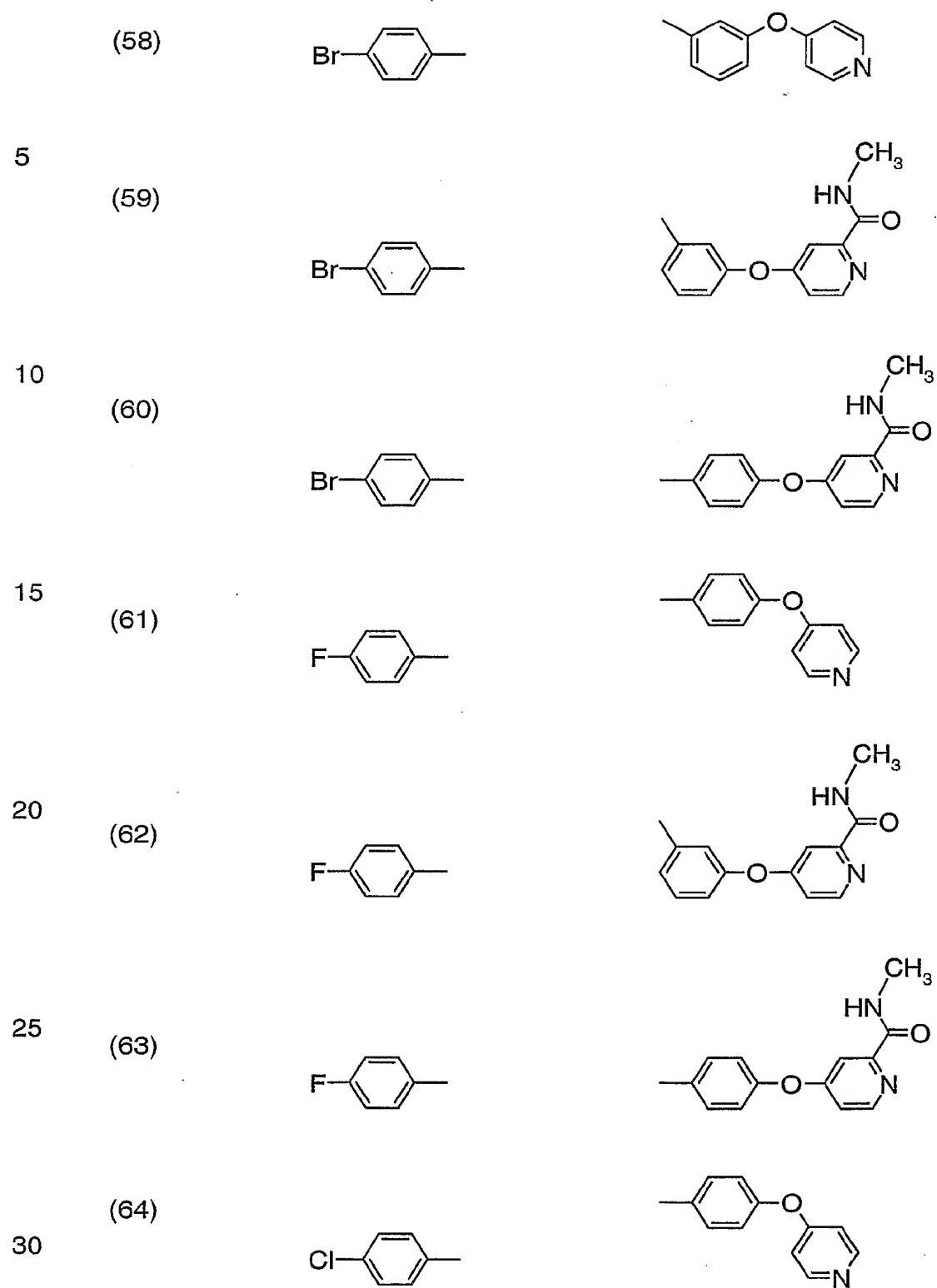


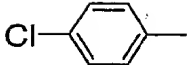
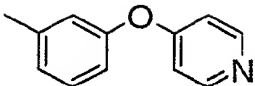
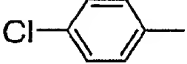
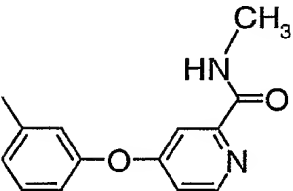
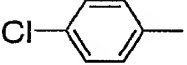
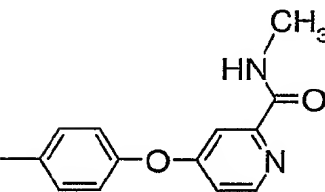
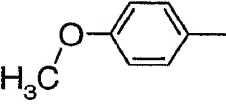
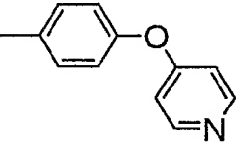
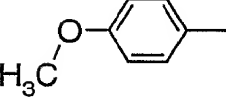
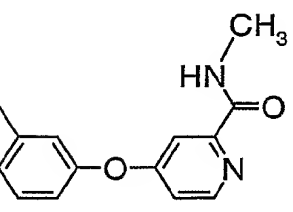
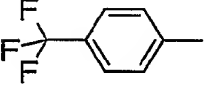
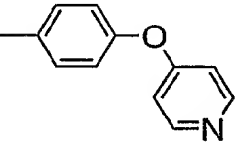
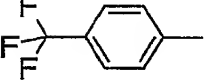
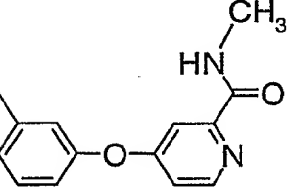
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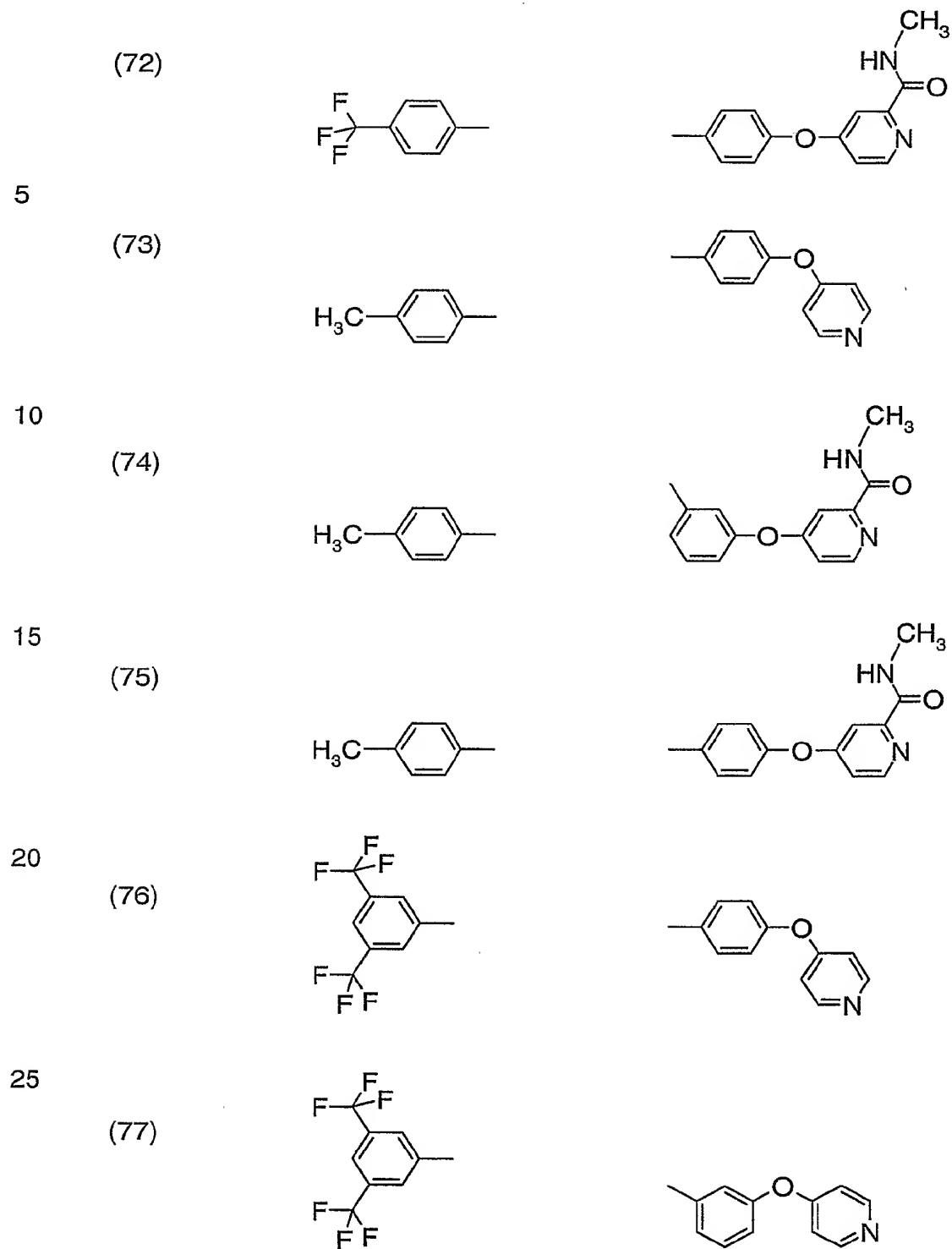


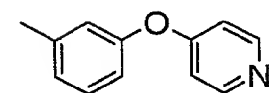
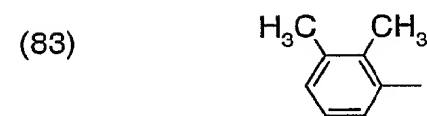
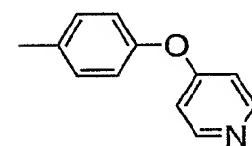
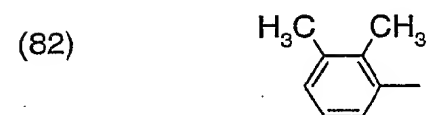
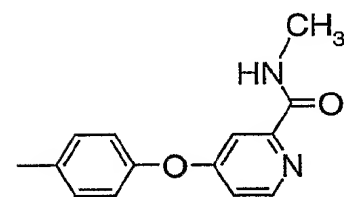
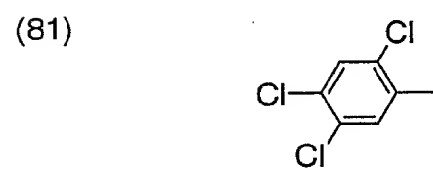
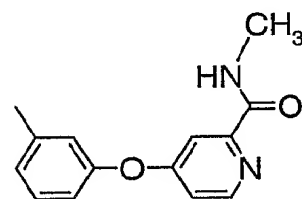
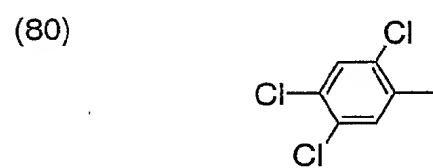
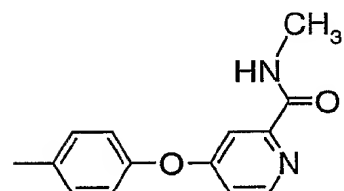
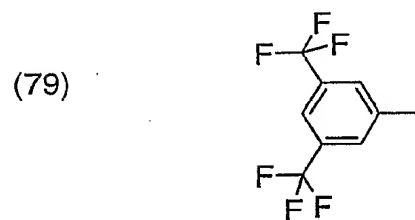
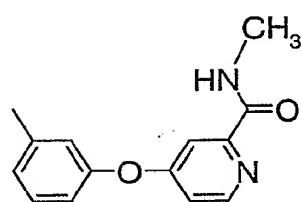
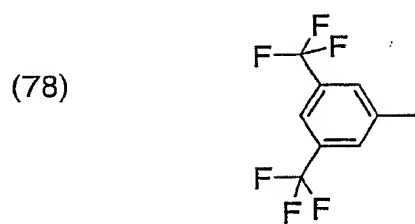
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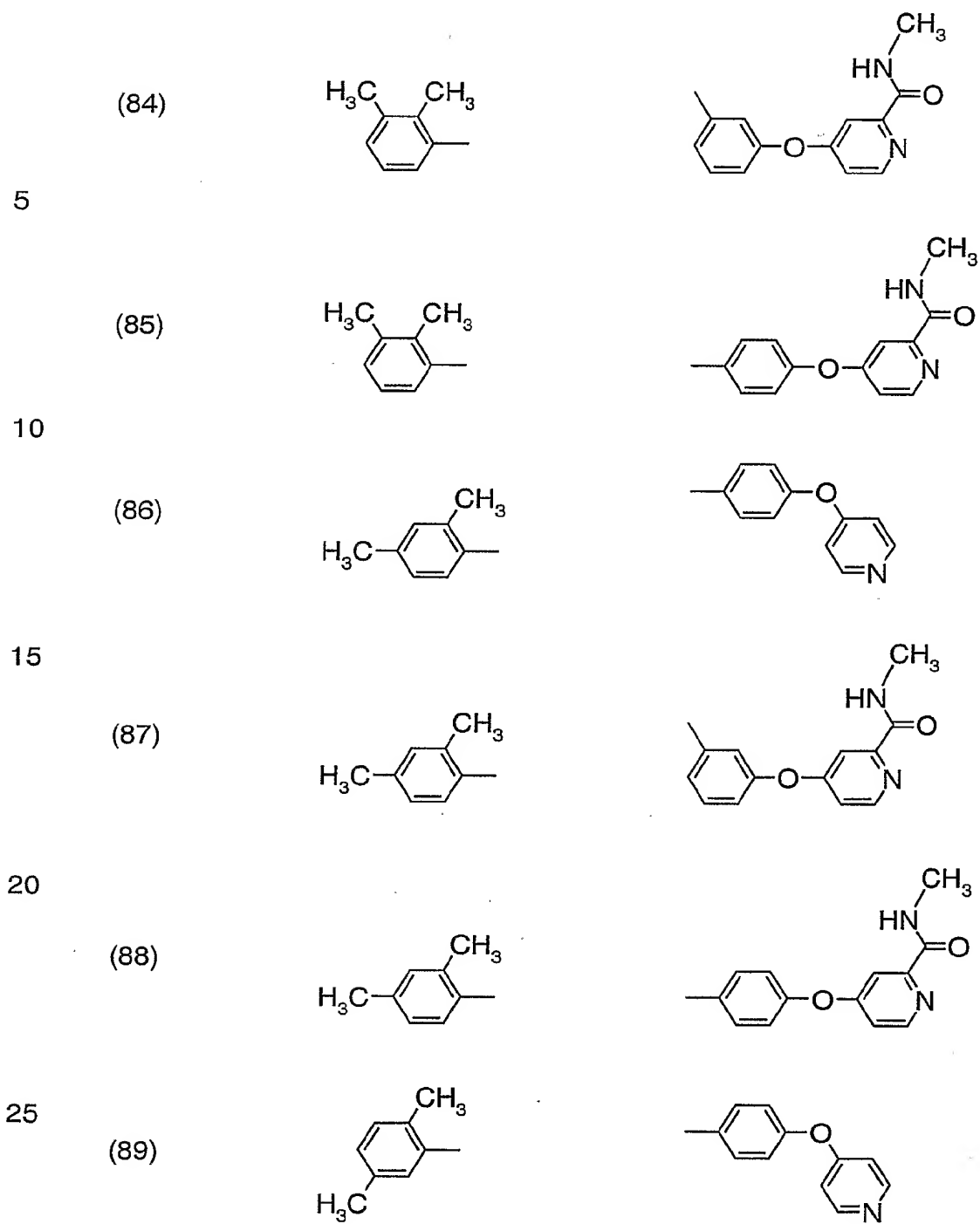
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20	(69)		
25	(70)		
30	(71)		



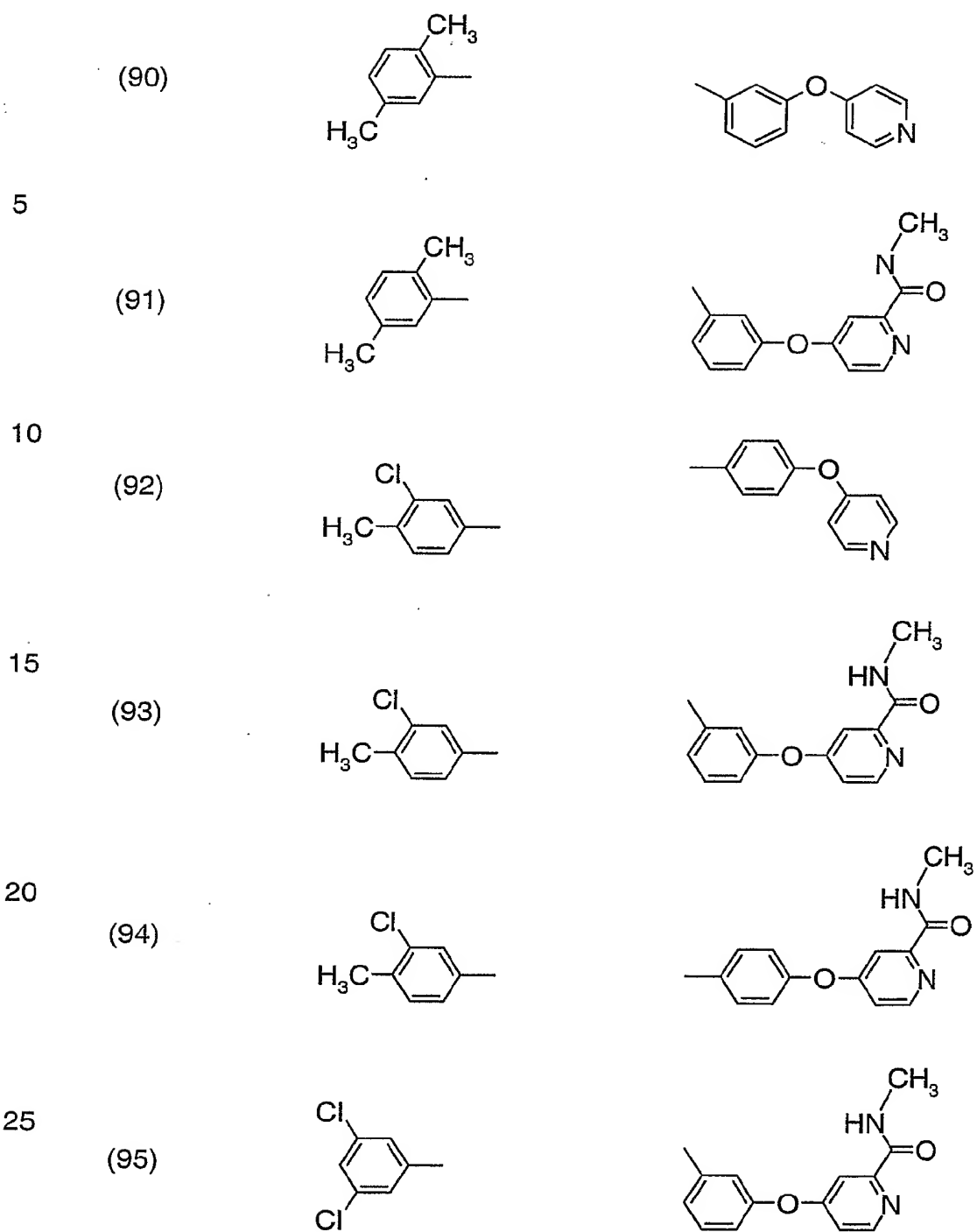


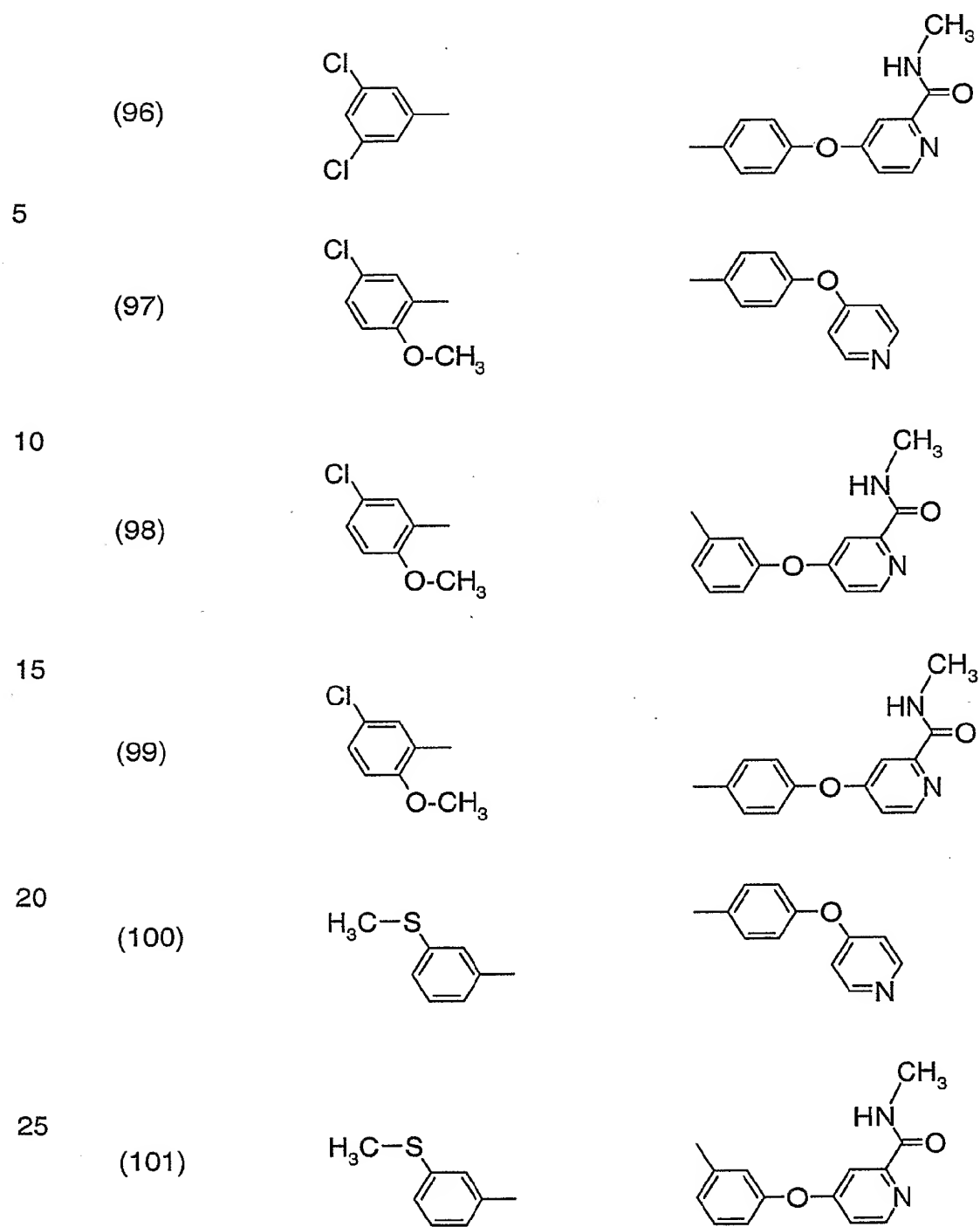


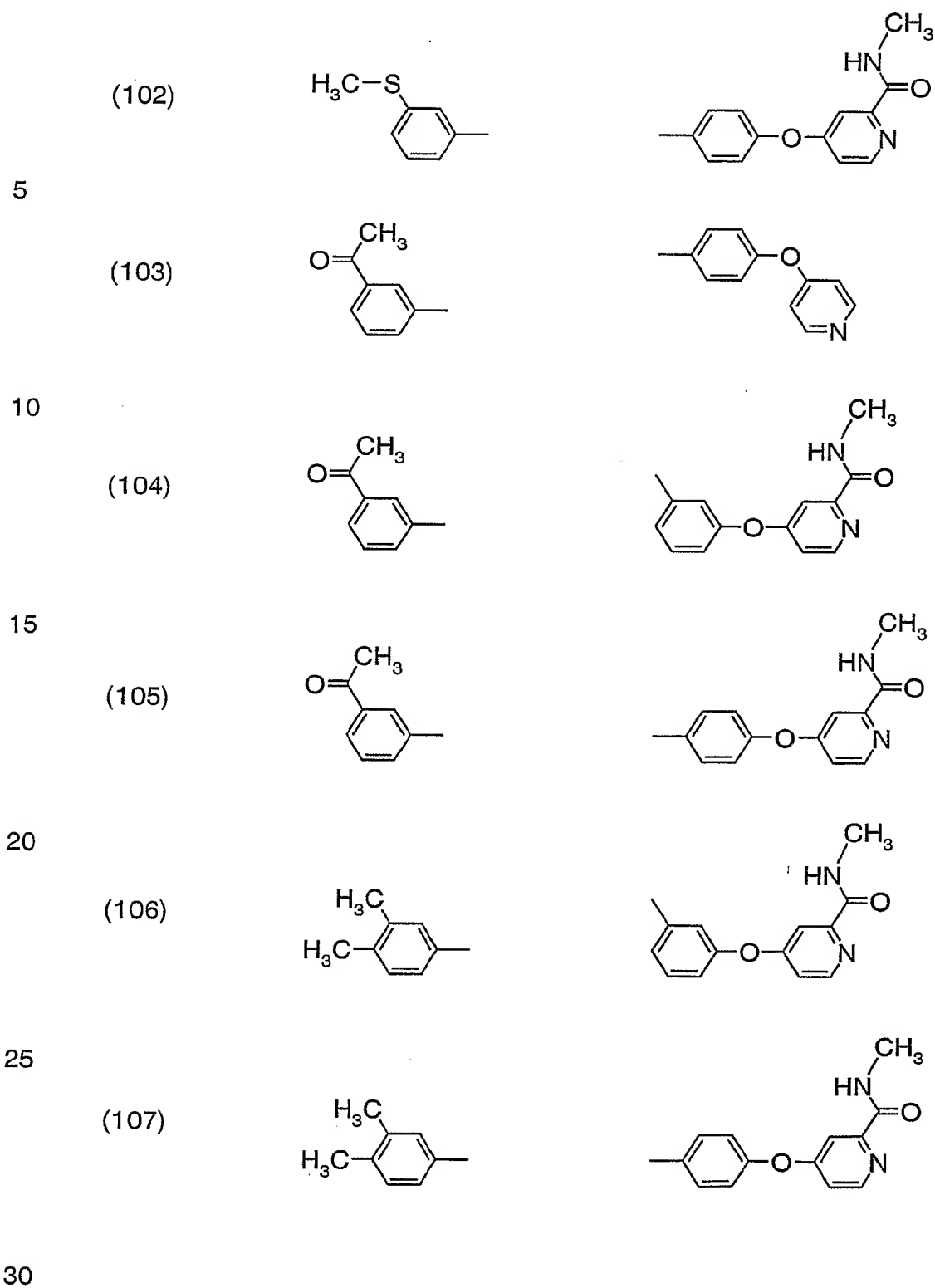
- 84 -



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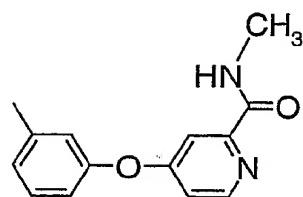
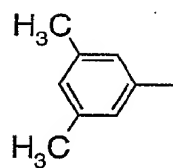






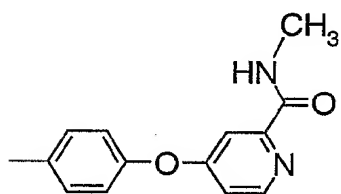
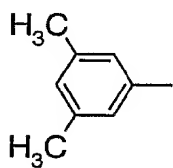
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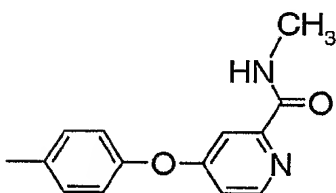
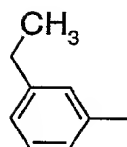
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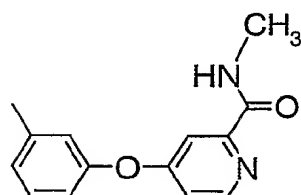
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(110)



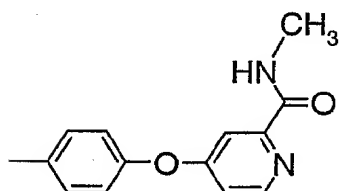
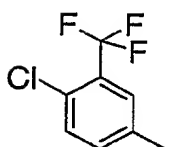
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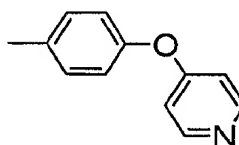
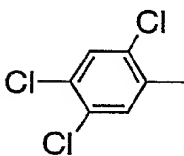
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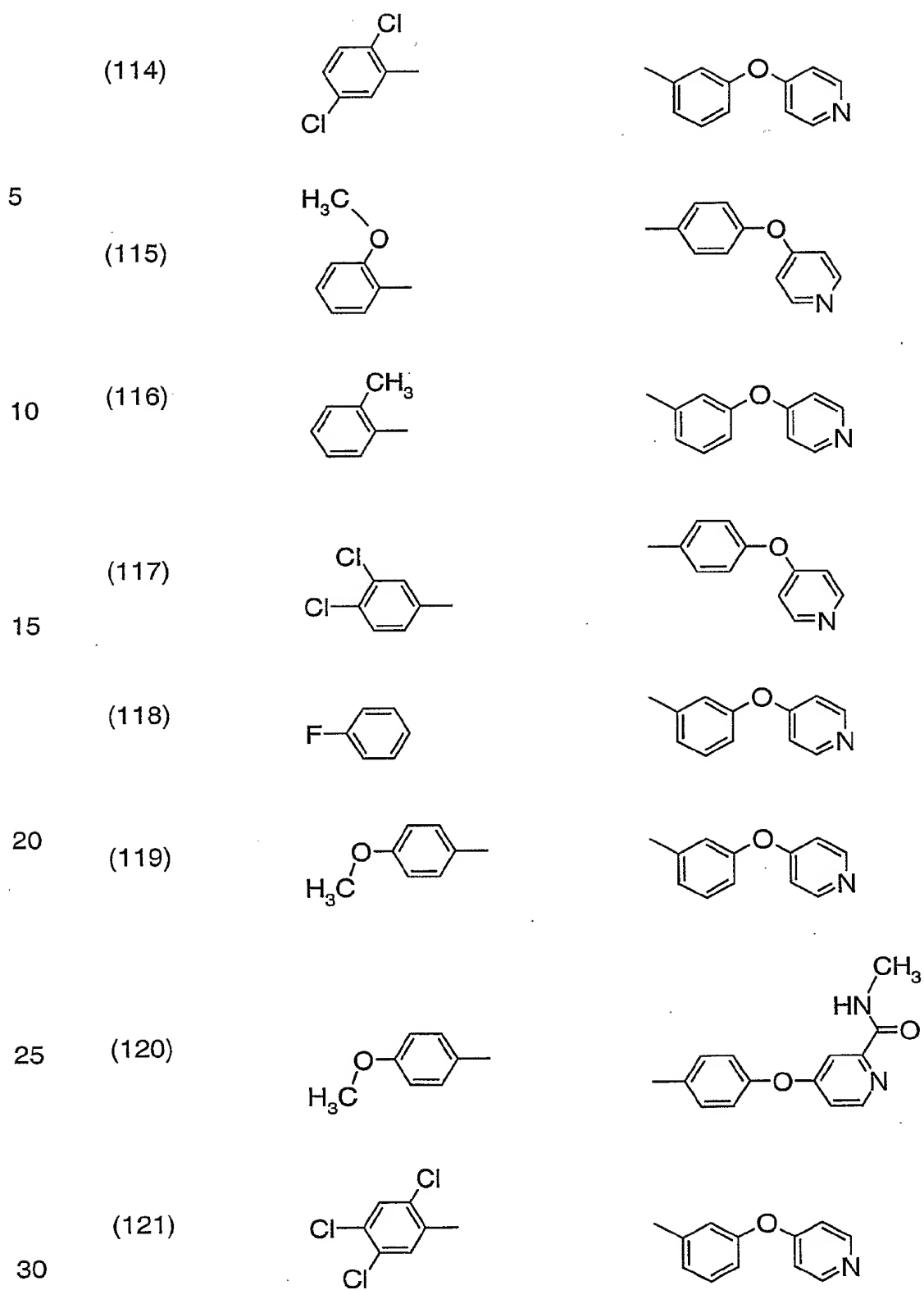
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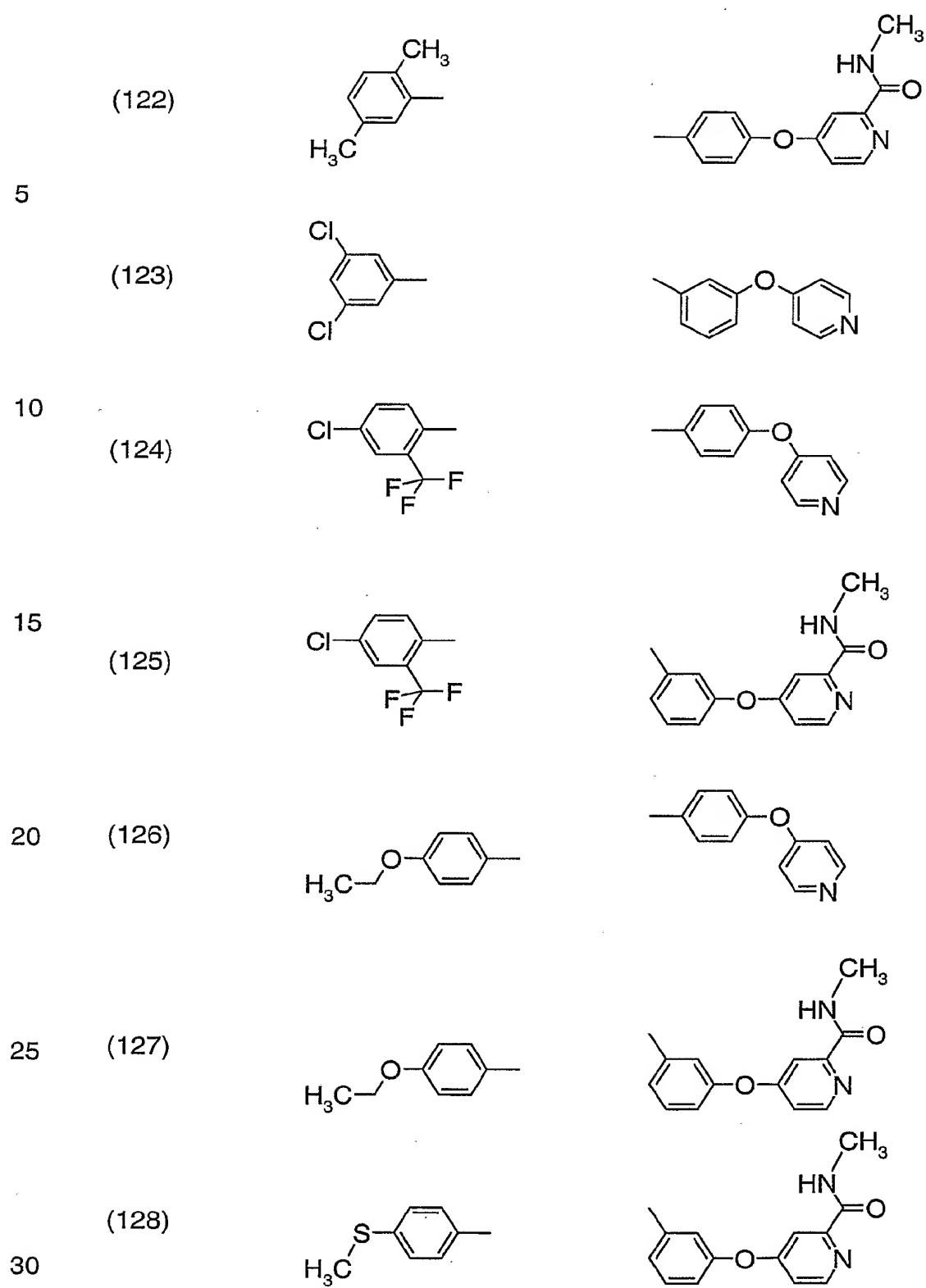


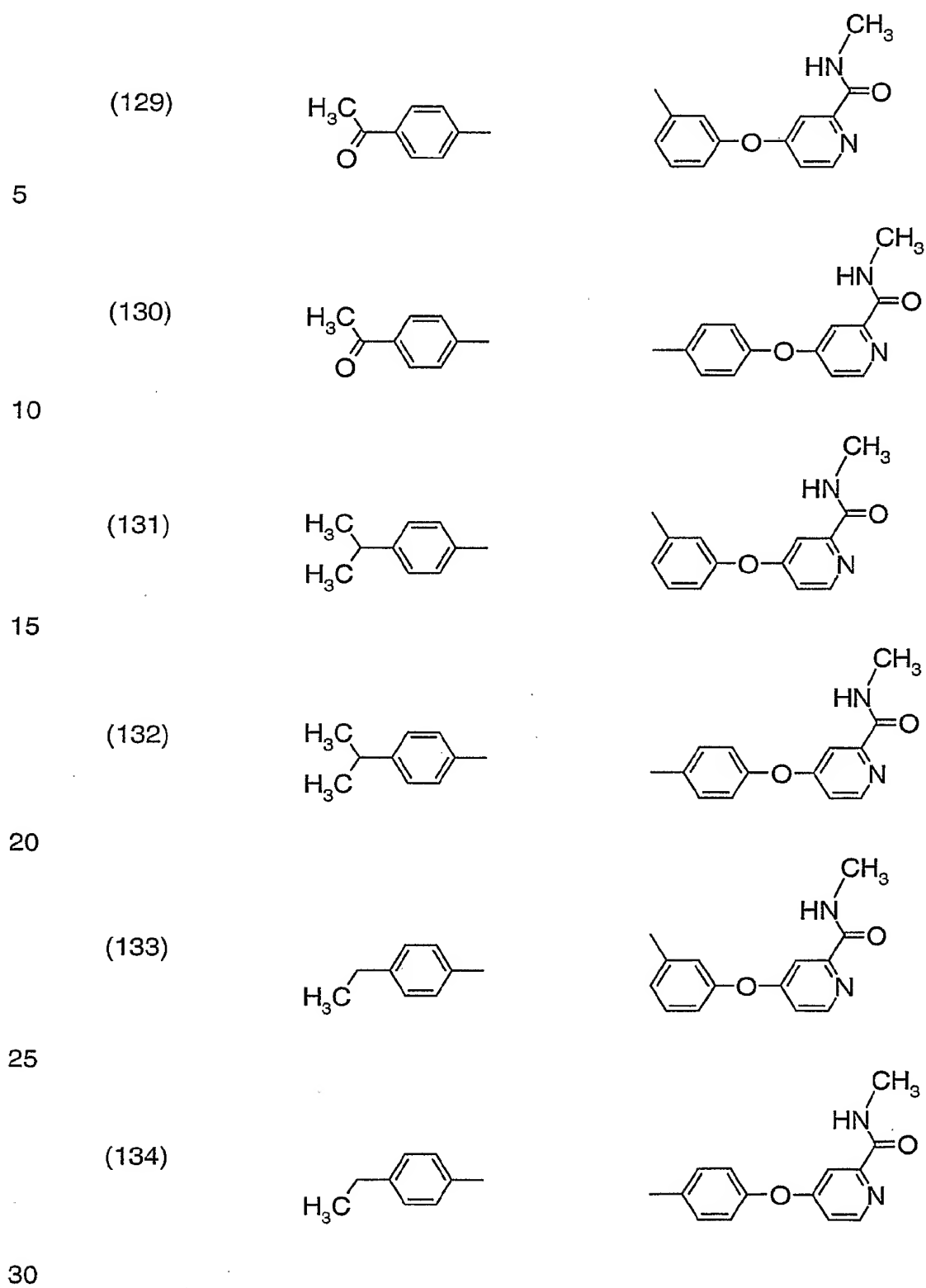
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(113)

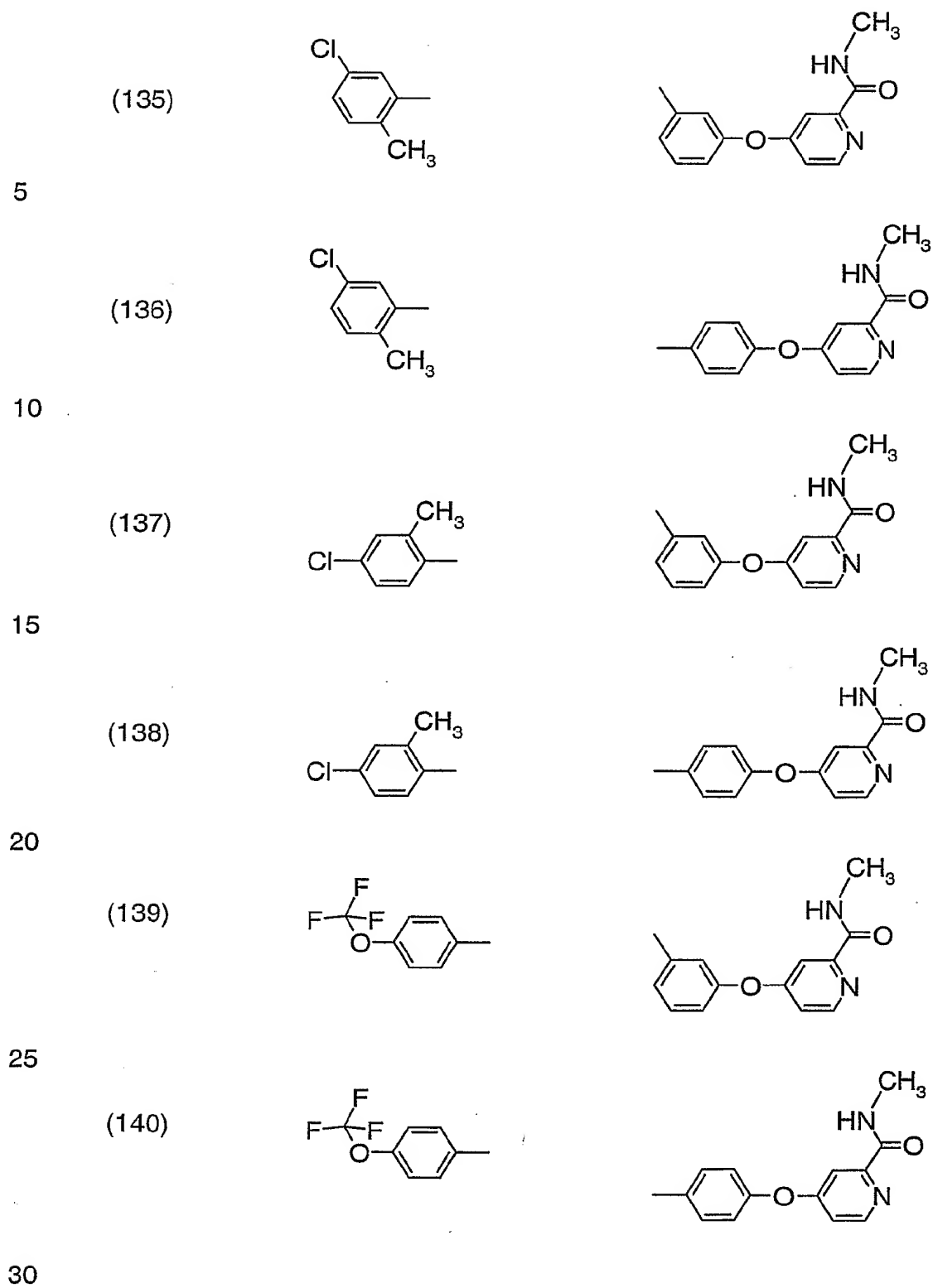


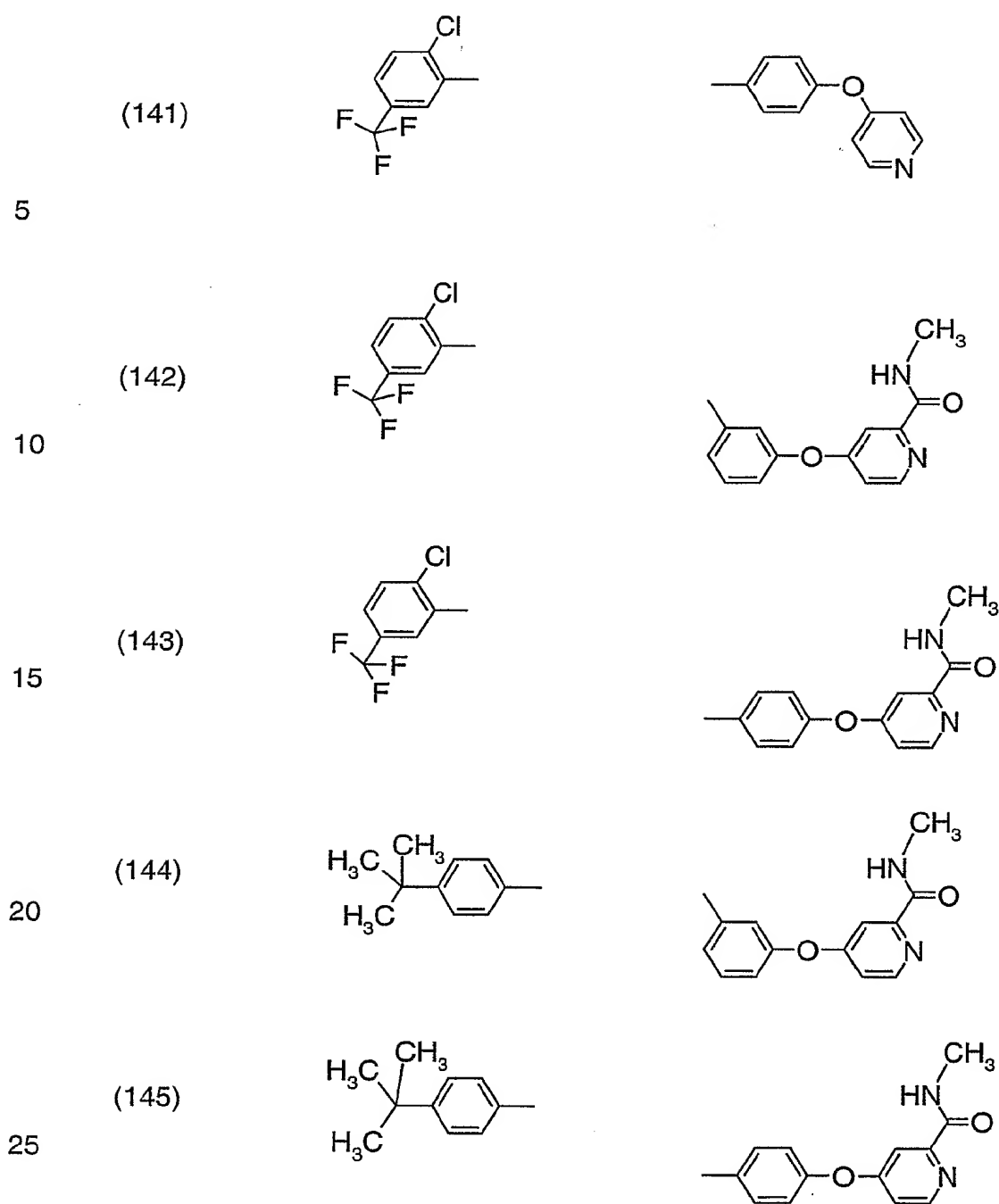




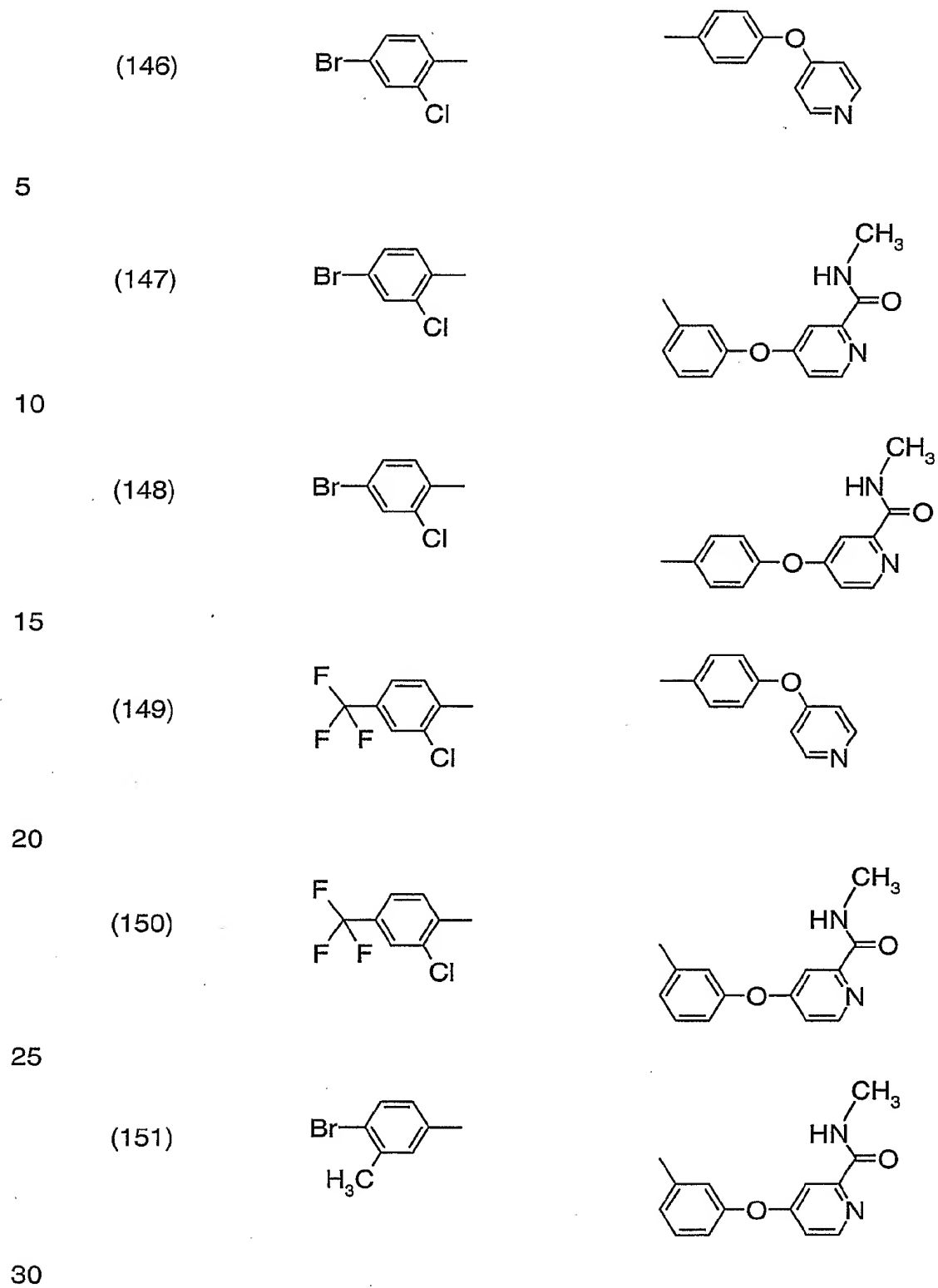


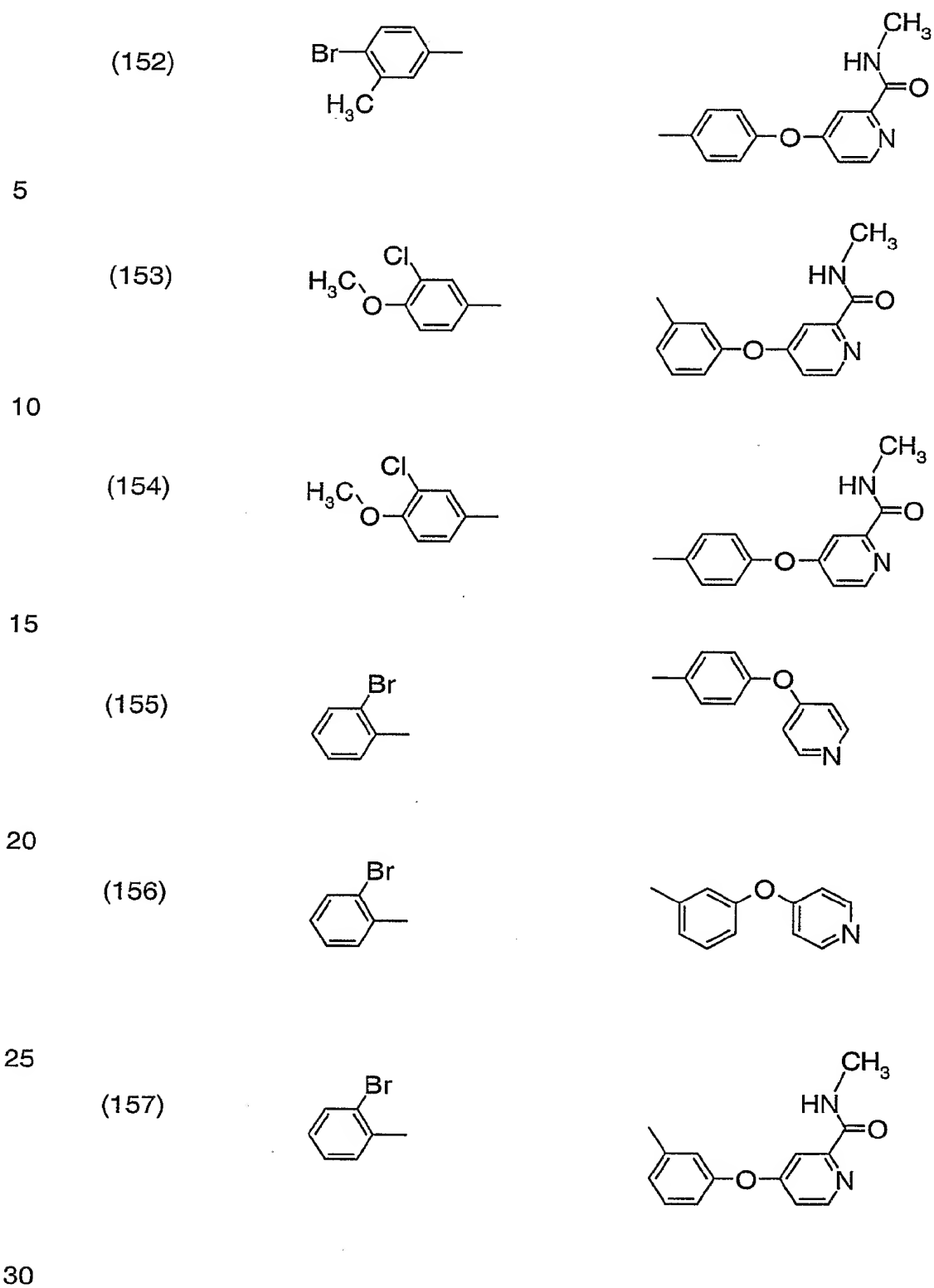




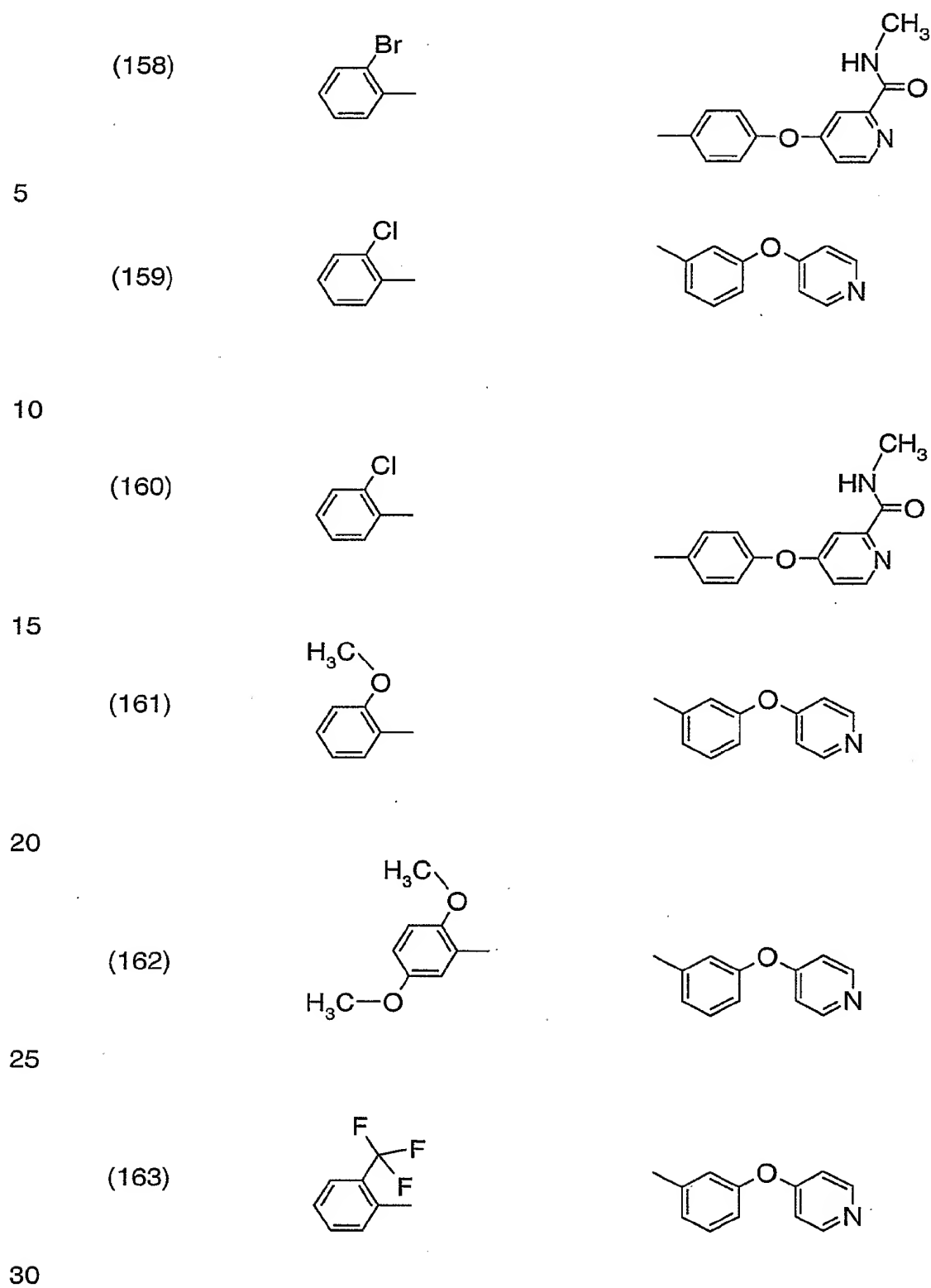


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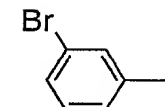
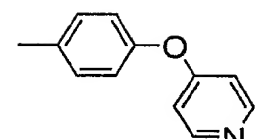
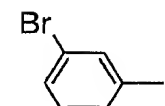
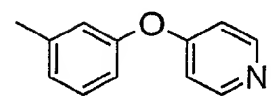
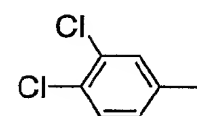
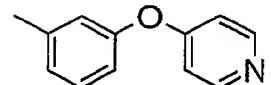
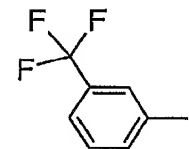
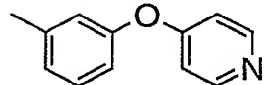
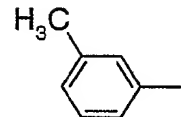
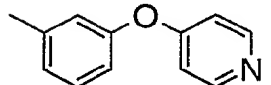
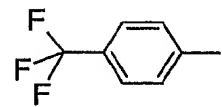
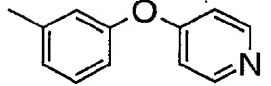
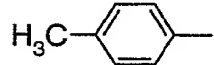
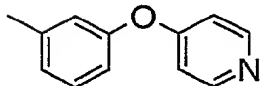




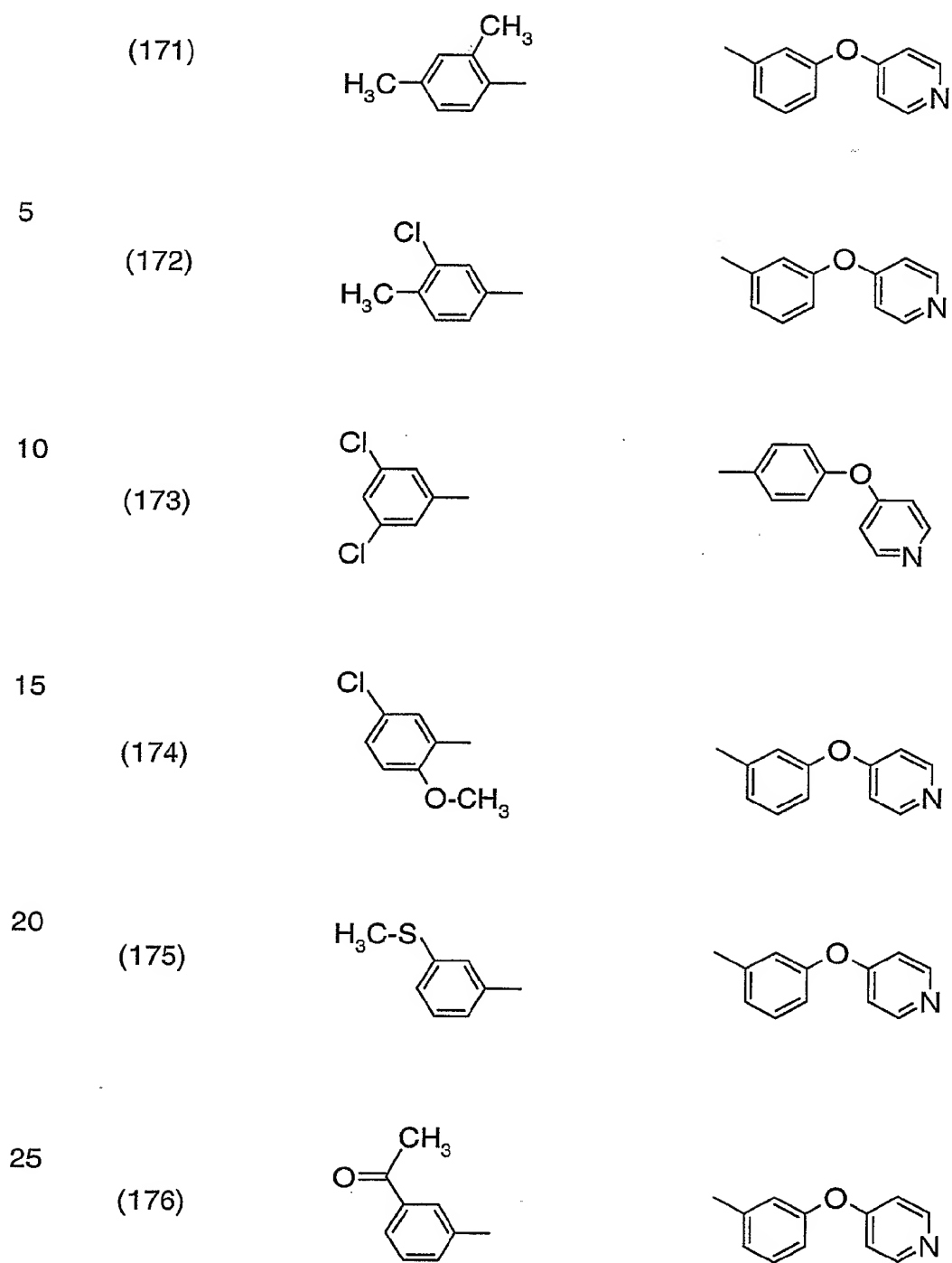
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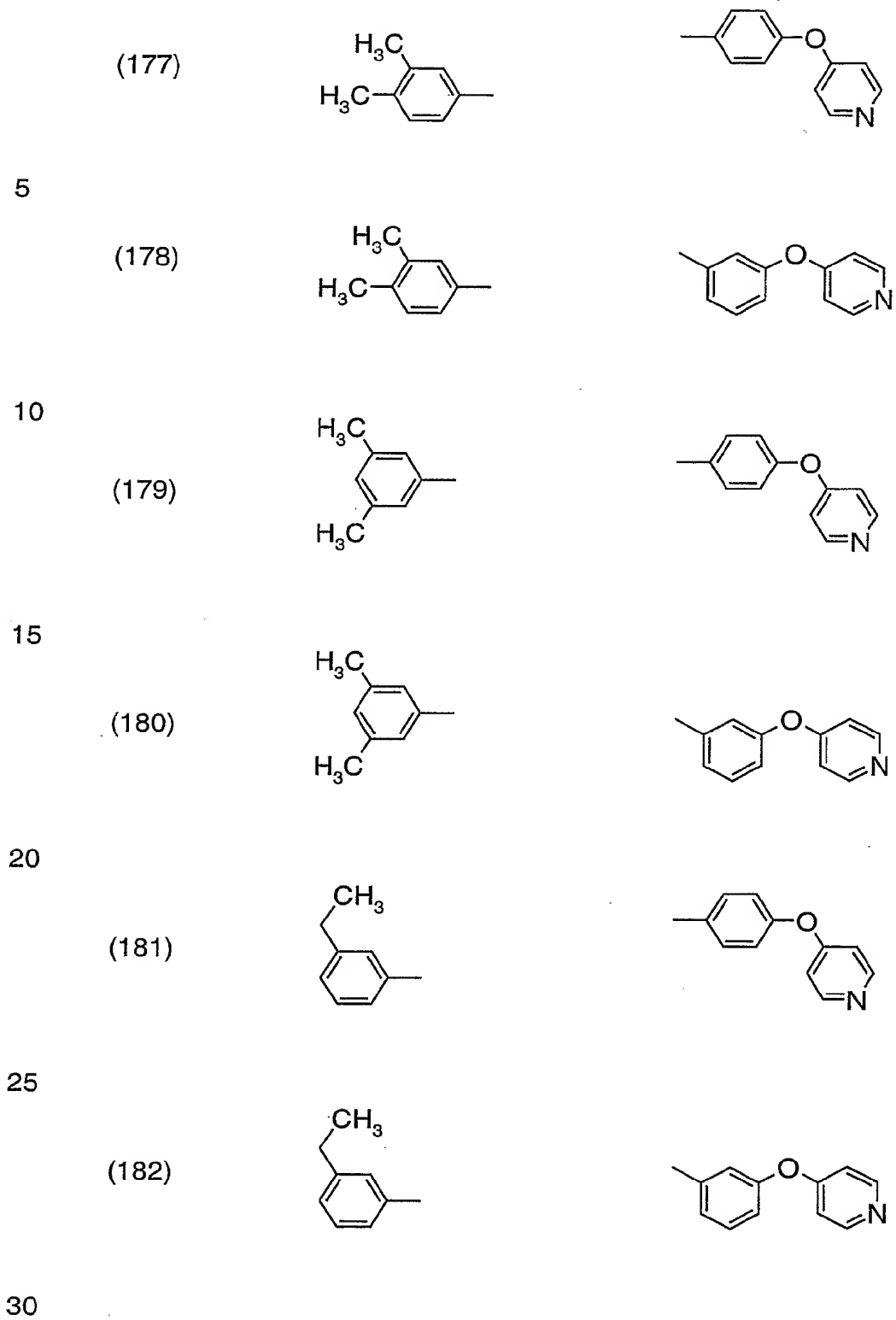
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	(170)		

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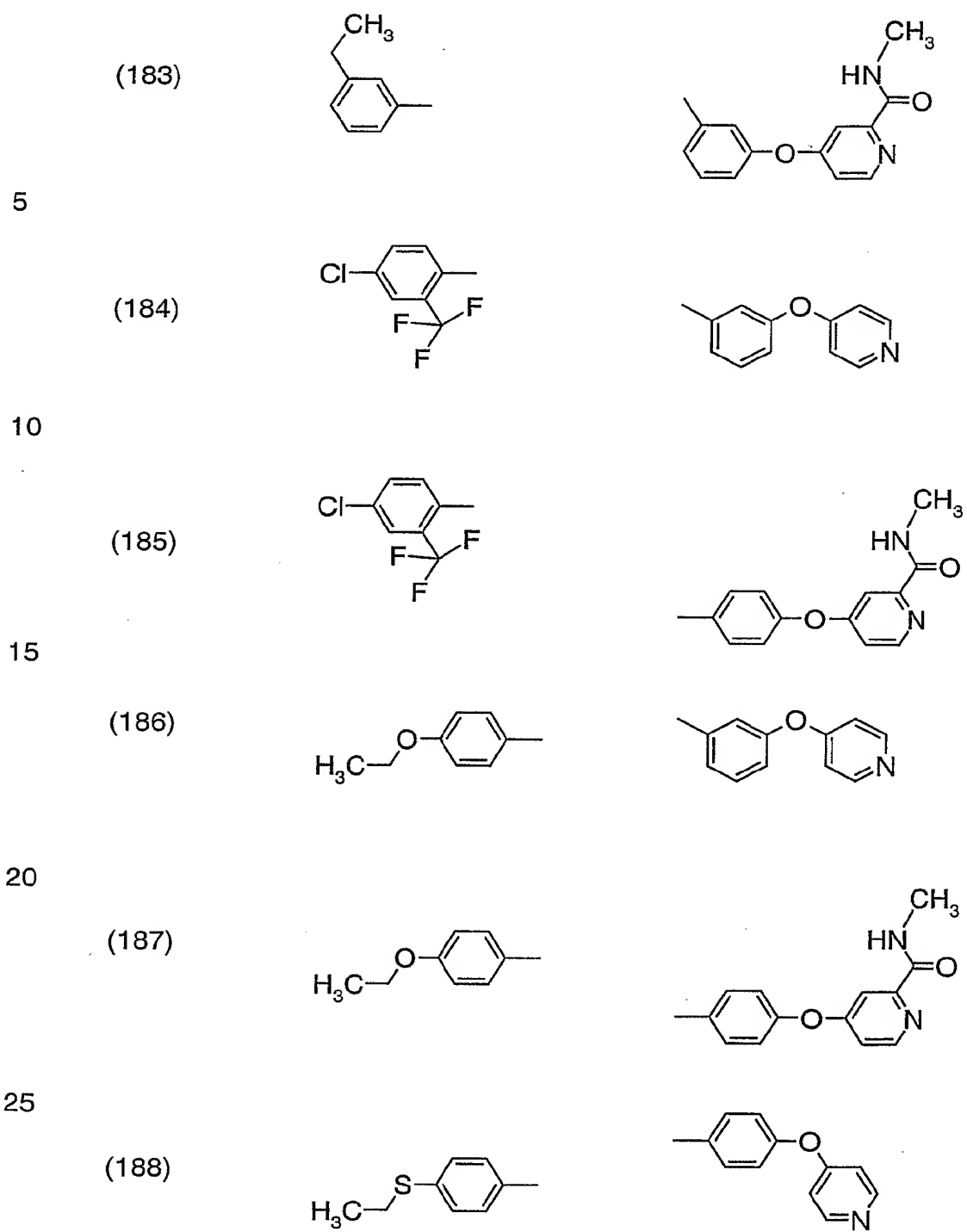


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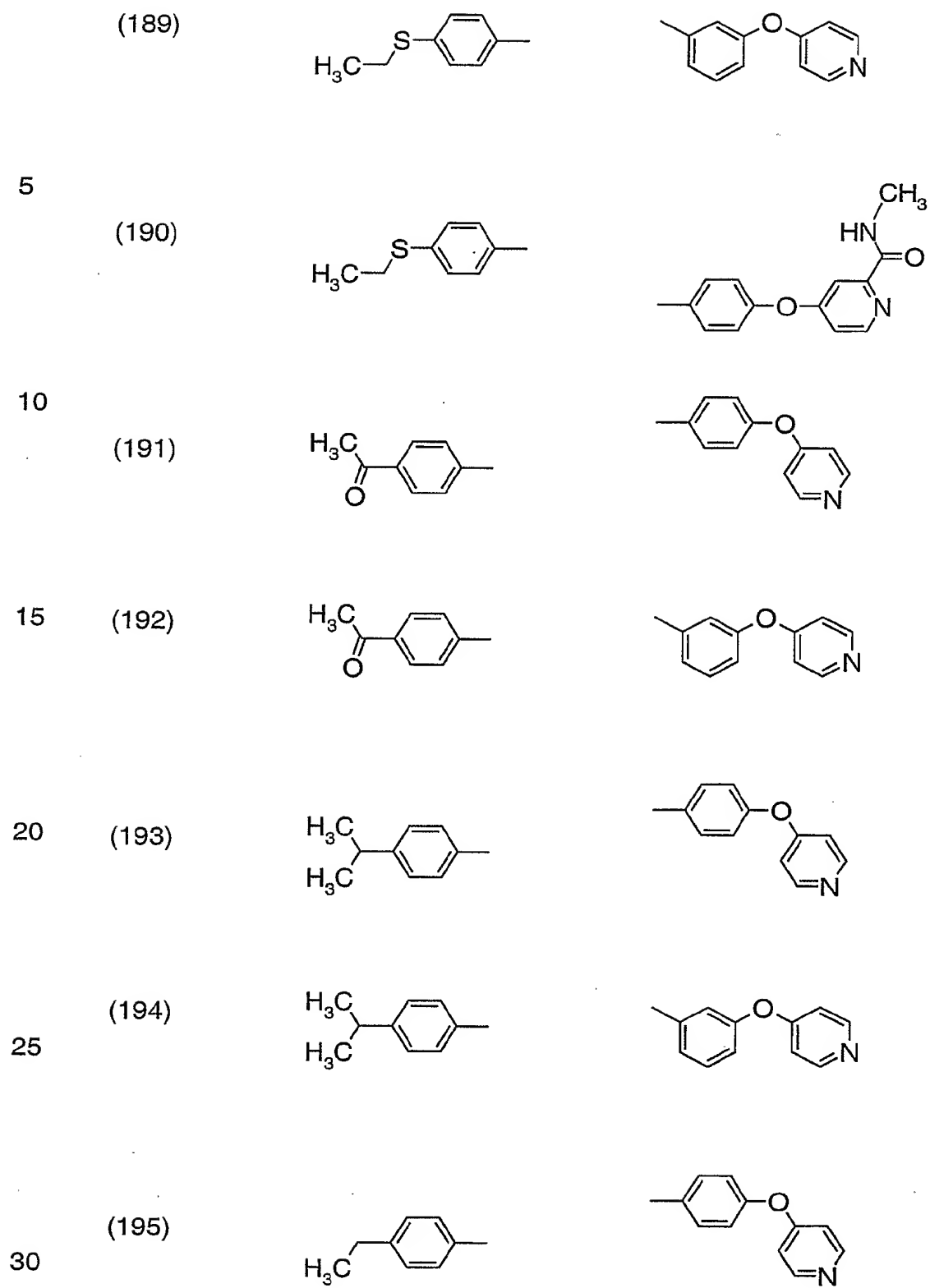
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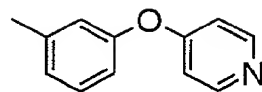
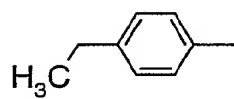




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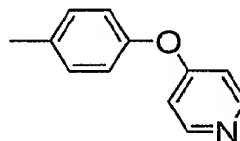
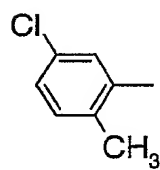


(196)



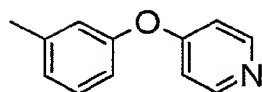
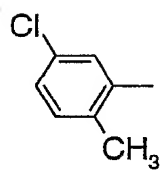
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(197)



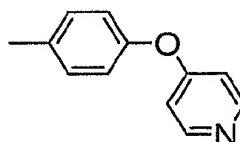
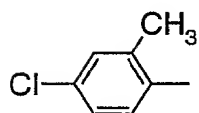
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(198)



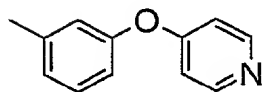
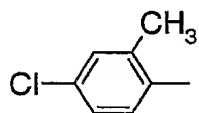
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(199)



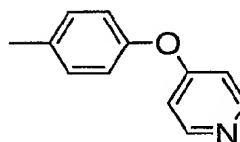
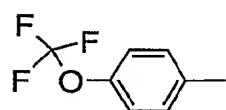
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(200)



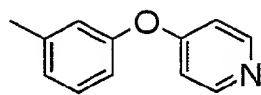
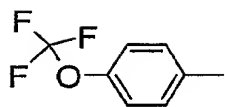
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(201)



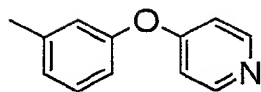
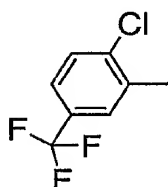
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(202)



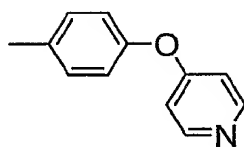
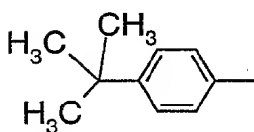
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(203)



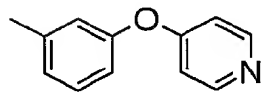
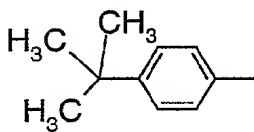
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(204)



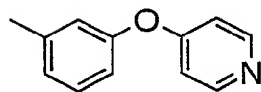
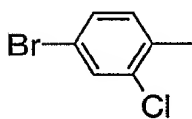
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(205)



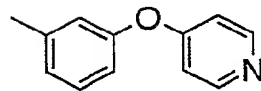
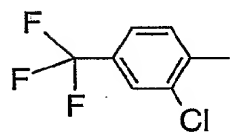
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(206)



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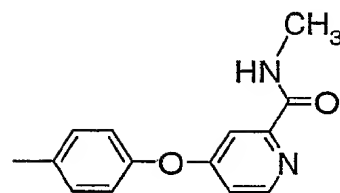
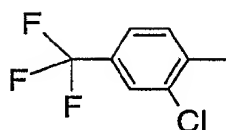
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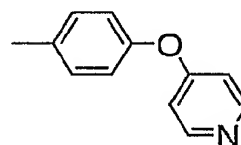
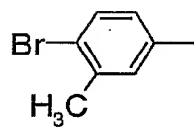
- 104 -

(208)



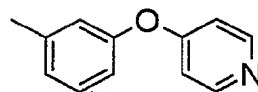
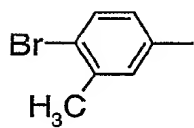
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(209)



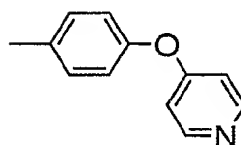
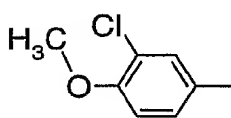
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(210)



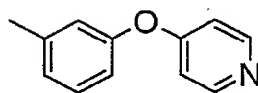
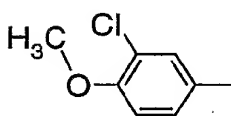
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(211)



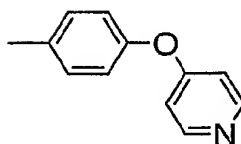
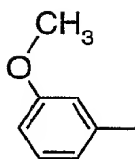
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(212)



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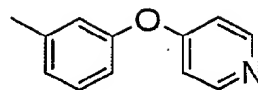
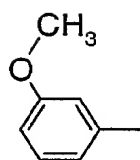
(213)



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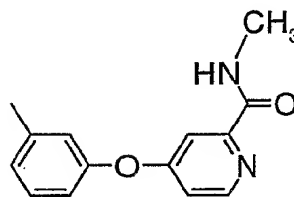
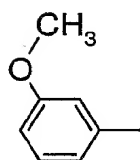
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(214)



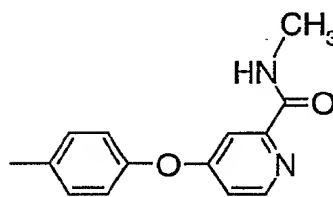
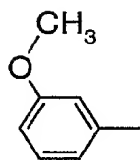
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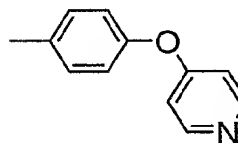
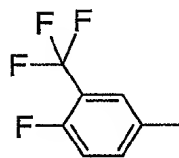
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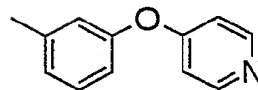
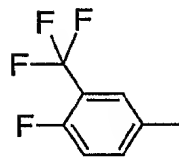
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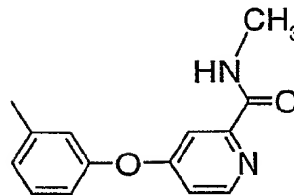
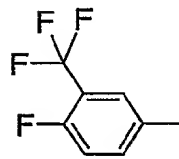
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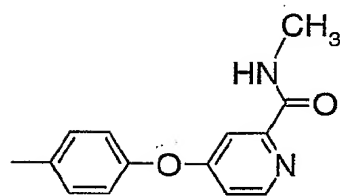
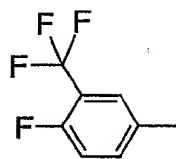
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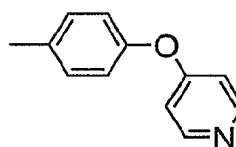
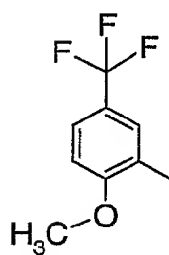
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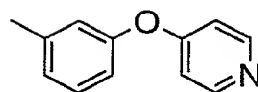
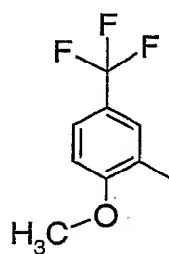
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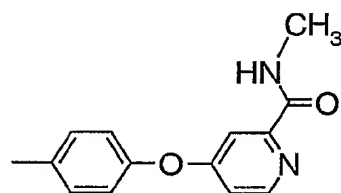
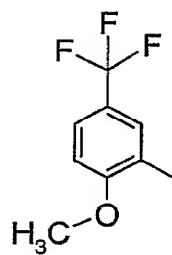
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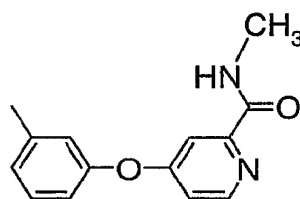
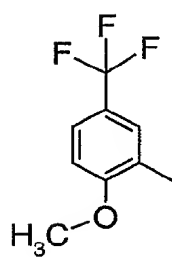
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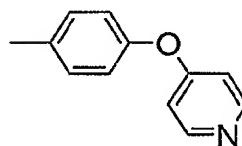
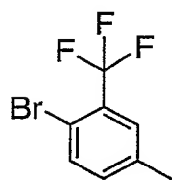
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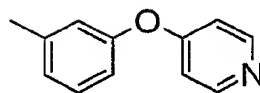
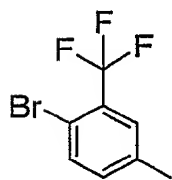
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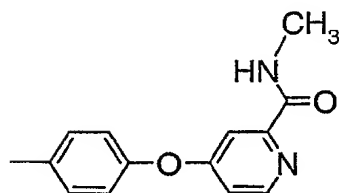
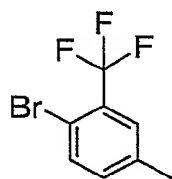
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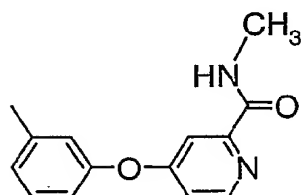
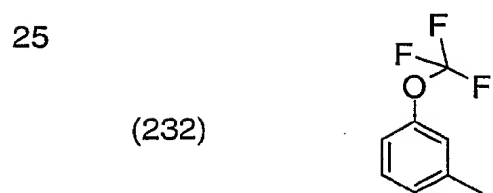
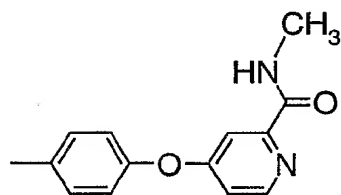
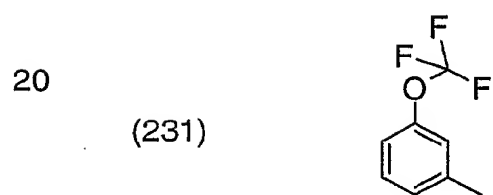
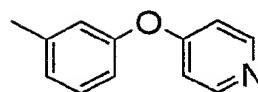
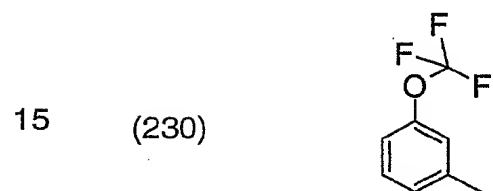
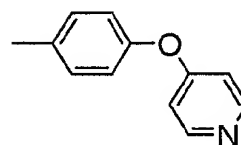
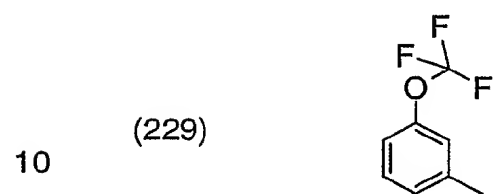
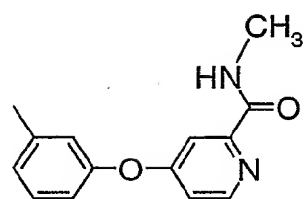
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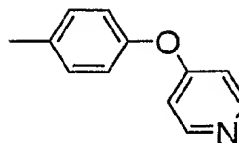
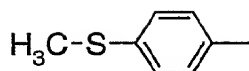
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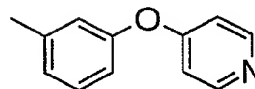
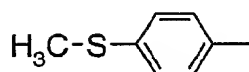
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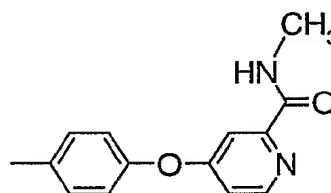
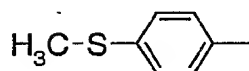
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In a special embodiment, the glycine derivatives according to sub formulae IIa, Ib, IIc, IId, IIe, IIg, IIh and/or compounds (1) to (235) additionally comprise one or two substituents selected from the group consisting of  $O(CH_2)_nNR^{11}R^{12}$ ,  $NR^{11}(CH_2)_nNR^{11}R^{12}$ ,  $O(CH_2)_nOR^{12}$  and  $NR^{11}(CH_2)_nOR^{12}$ ,

20

wherein

$R^{11}$ ,  $R^{12}$  are independently selected from a group consisting of H, A,  $(CH_2)_mAr^3$  and  $(CH_2)_mHet$ , or in  $NR^{11}R^{12}$ ,

$R^{11}$  and  $R^{12}$  form, together with the N-Atom they are bound to, a 5-, 6- or 7-membered heterocycle which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S, and n is 1, 2, 3, 4, 5 or 6, preferably 2, 3 or 4.

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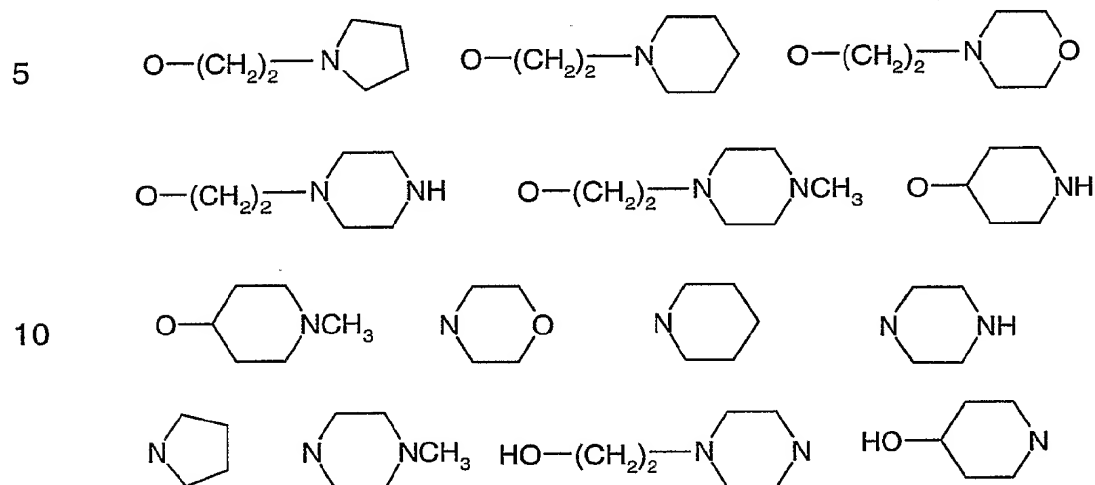
n

In this embodiment, the substituents are preferably selected from the group consisting of  $HNCH_2CH_2NH_2$ ,  $OCH_2CH_2NH_2$ ,  $NHCH_2CH_2OH$ ,  $OCH_2CH_2NHCH_3$ ,  $N(CH_3)CH_2CH_2NH_2$ ,  $HN(CH_3)CH_2CH_2NH$ ,

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$N(CH_3)CH_2CH_2N(CH_3)_2$ ,  $N(CH_3)CH_2CH_2N(CH_3)_2$ ,  $N(CH_3)CH_2CH_2OCH_3$ ,  
 $OCH_2CH_2N(CH_3)_2$ ,  $OCH_2CH_2N(CH_2CH_3)_2$  and compounds of the formulae



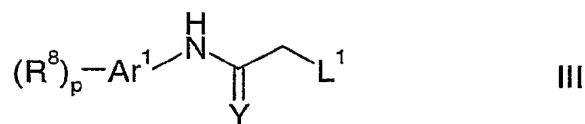
In this embodiment, the additional substituents are preferably bound to one of the aromatic residues directly bound to the glycine moiety and/or the pyridinyl residue. Preferably, one additional substituent is bound to the aromatic residue directly bound to the amide-nitrogen atom of the glycine moiety and/or one additional substituent is bound to the pyridinyl residue.

The nomenclature as used herein for defining compounds, especially the compounds according to the invention, is in general based on the rules of the IUPAC-organisation for chemical compounds and especially organic compounds.

Another aspect of the invention relates to a method for producing compounds of formula II, characterised in that

a) A compound of formula III

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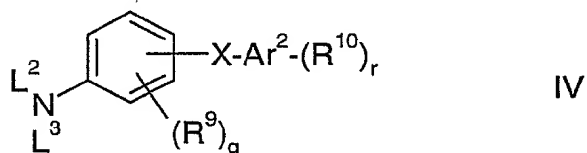


wherein

$L^1$  is Cl, Br, I, OH, a reactive esterified OH-group or a diazonium moiety, and  $R^8$ ,  $p$ ,  $Ar^1$ ,  $Y$  are as defined above and below,

is reacted

b) with a compound of formula IV,



wherein

$L^2$ ,  $L^3$  are independently from one another H or a metal ion, and  $R^9$ ,  $q$ ,  $X$ ,  $Ar^2$ ,  $R^{10}$  and  $r$  are as defined above and below,

and optionally

c) isolating and/or treating the compound of formula II obtained by said reaction with an acid, to obtain the salt thereof.

The compounds of the formula I and preferably the compounds of the formula II and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der

organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

5

If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I or II, respectively. On the other hand, it is possible to carry out the reaction stepwise.

10

The compounds of the formula I and especially the compounds of formula II can preferably be obtained by reacting compounds of the formula III with compounds of the formula IV.

15

In detail, the reaction of the compounds of the formula III with the compounds of the formula IV is carried out in the presence or absence of a preferably inert solvent at temperatures between about  $-20^{\circ}$  and about  $200^{\circ}$ , preferably between  $0^{\circ}$  and  $150^{\circ}$  and especially between room temperature ( $25^{\circ}$ ) and  $120^{\circ}$ . In many cases, it is advantageous to combine one compound of formula III with one compound of formula IV at the lower end of the given temperature range, preferably between  $-20^{\circ}$  and  $75^{\circ}$ , more preferred between  $0^{\circ}$  and  $60^{\circ}$  and especially between  $10^{\circ}$  and  $40^{\circ}$ , for example at about room temperature, and heat the mixture up to a temperature at the upper end of the given temperature range, preferably between  $80^{\circ}$  and  $180^{\circ}$ , more preferred between  $90^{\circ}$  and  $150^{\circ}$  and especially between  $95^{\circ}$  and  $120^{\circ}$ , for example at about  $100^{\circ}$  or at about  $110^{\circ}$ .

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In general, the compounds of formula III and/or formula IV are new. In any case, they can be prepared according to methods known in the art or analogous to those procedures.

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In the compounds of formula III,  $L^1$  is preferably Cl, Br, I, OH, a reactive derivatized OH-moiety, especially a reactive esterified OH-moiety, for example an alkylsulfonyloxy-moiety comprising 1 to 6 carbon atoms (preferably methylsulfonyloxy) or and arylsulfonyloxy-moiety comprising 6 to 10 carbon atoms (preferably phenyl- or p-tolylsulfonyloxy), or diazonium moiety, more preferred Cl, Br or I and even more preferred Cl.

In the compounds of formula IV,  $L^2$  and/or  $L^3$  is preferably H or a moiety which activates the amino group it is bonded to, for example a metal ion. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions. Especially preferred metal ions are alkaline metal ions, of which Li, Na and K are especially preferred. In case of multi-valent metal ions, the metal ions and the compounds of formula IV form a complex containing one or more compounds of formula IV and one or more metal ions wherein the ratio between compounds of formula IV and metal ions is depending on the valency of the metal ion(s) according to the rules of stoichiometry and/or electroneutrality.

The reaction between the compounds of formula III and compounds of formula IV is preferably carried out in the presence of an acid binding means, for example one or more bases. Suitable acid binding means are known in the art. Preferred as acid binding means are inorganic bases and especially organic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Examples for organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction. Especially preferred as organic base is diisopropyl ethyl amine.

Reaction times are generally in the range between some minutes and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily  
5 determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range 10 min and 24 hrs, preferably 30 min and 12 hrs and especially between 45 min and 8 hrs, for example about 1 h, about 2 hrs, about 4 hrs or about 6 hrs.

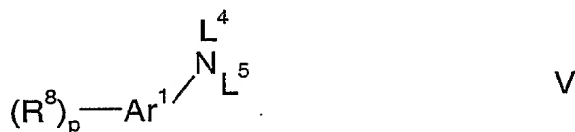
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Preferably, the reaction of the compounds of the formula III with the compounds of the formula IV is carried out in the presence of a suitable solvent, that is preferably inert under the respective reaction conditions. Examples of suitable solvents are hydrocarbons, such as hexane,  
15 petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers,  
20 such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters,  
25 such as ethyl acetate, or mixtures of the said solvents. Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and sulfoxides or mixtures thereof. More preferred are amides, especially dimethylform-  
amide (DMF).

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The compounds of formula III can be obtained according to methods known in the art. In an advantageous manner, they can be readily obtained by reacting a compound of formula V



wherein  $R^8$ ,  $p$ , and  $Ar^1$  are as defined above/below and  $L^4$  and  $L^5$  are selected independently from each other from the meanings given for  $L^2$  and  $L^3$  and more preferred are hydrogen, with a compound of formula VI



wherein  $Y$  is as defined above/below and  $L^6$  and  $L^7$  are selected independently from each other from the meanings given for  $L^1$ . Preferably,  $L^6$  and/or  $L^7$  are halogen. More preferred, both  $L^6$  and  $L^7$  are independently selected from the group consisting of Cl, Br and I. Especially preferred, both  $L^6$  and  $L^7$  are Cl.

Some of the starting materials of the formula V and/or the formula VI are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

Suitable reaction conditions for carrying out reaction of compounds of formula V with compounds of formula VI are known in the art. In detail, the reaction of the compounds of the formula V with the compounds of the formula VI is carried out in the presence or absence of a preferably inert solvent at temperatures between about  $-40^\circ$  and about  $180^\circ$ , preferably between  $-20^\circ\text{C}$  and  $100^\circ$  and especially between  $-10^\circ$  and  $50^\circ$ , for



example at about 0° and/or about room temperature (25°). In many cases, it is advantageous to combine one compound of formula V with one compound of formula VI at the lower end of the given temperature range, preferably between -20° and 40°, more preferred between -10° and 20° and especially between -5° and 10°, for example at about 0°, and heat the mixture up to a temperature at the upper end of the given temperature range, preferably between 20° and 150°, more preferred between 20° and 100° and especially between 20° and 50°, for example at about room temperature.

10

The reaction between compounds of formula V and compounds of formula VI is preferably carried out in the presence of an acid binding means, for example one or more bases. Suitable acid binding means are known in the art. Preferred as acid binding means are inorganic bases and especially organic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Examples for organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction. Especially preferred as organic base is pyridine.

20

The reaction between compounds of formula V and compounds of formula VI can be carried out in the presence of a suitable solvent, that is preferably inert at the chosen reaction conditions. Suitable solvents are known in the art. Examples of suitable solvents include hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; nitriles,

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such as acetonitrile; esters, such as ethyl acetate, or mixtures of the aid solvents. Non-protic solvents are in general preferred.

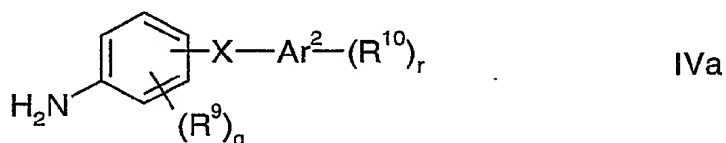
If the reaction between a compound of formula V and a compound of formula VI is carried out in presence of an organic base that is liquid at the chosen reaction conditions, preferably no additional solvent is used.

The compounds of formula IV can be obtained according to methods known in the art.

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If the compound of formula IV is a compound according to formula IVa,

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it can be readily obtained in an advantageous manner by reacting a compound of formula VIIa,

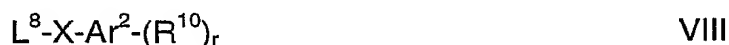
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wherein  $R^9$  and  $q$  are as defined above/below,

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with a compound of formula VIII,



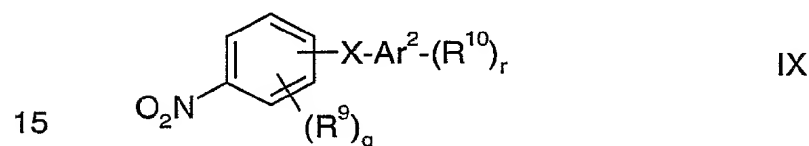
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wherein  $L^8$  is H or a metal ion, preferably a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and

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aluminum ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred, and even more preferred is H; and  $\text{Ar}^2$ ,  $\text{R}^{10}$ ,  $r$  and  $X$  are as defined above/below, and especially wherein  $X$  is  $(\text{CHR}^{11})_h\text{-Q-(CHR}^{12})_i$ , wherein  $\text{R}^{11}$ ,  $h$  and  $\text{R}^{12}$  are defined above/below,  $j$  is 0 and  $Q$  is selected from a group consisting of O, S,  $\text{N-R}^{15}$ ,  $(\text{CHR}^{18}\text{-O})_j$ ,  $(\text{CHR}^{18}\text{CHR}^{19}\text{-O})_j$ ,  $\text{CH=N-O}$ ,  $\text{CH=N-NR}^{15}$ ,  $\text{SO}_2\text{NR}^{15}$ , wherein  $\text{R}^{15}$ ,  $\text{R}^{18}$  and  $\text{R}^{19}$  are as defined above/below;

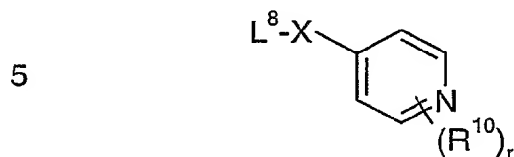
optionally isolating the reaction product,  
and transferring the obtained reaction product of formula IX



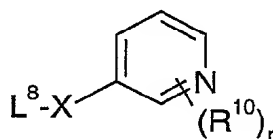
into a compound of formula IVa, preferably by hydrogenating the  $\text{NO}_2$ -moiety of the compound of formula IX into a  $\text{NH}_2$ -moiety. Methods and reaction conditions for hydrogenating said  $\text{NO}_2$ -moiety into a  $\text{NH}_2$ -moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, preferably a Palladium catalyst, for example Pd/C. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol and ethers, especially THF, and mixtures thereof. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between  $-20^\circ$  and  $150^\circ$ , preferably  $0^\circ$  and  $50^\circ$ .

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Ar<sup>2</sup> is preferably pyridinyl. Accordingly, the compound of formula VIII is preferably selected from the group consisting of formulae VIIIa and VIIIb,

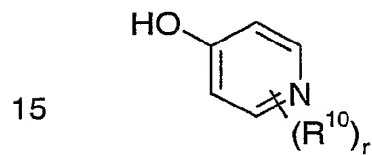


VIIIa

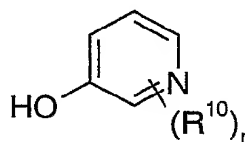


VIIIb

10 wherein L<sup>8</sup>, X, R<sup>10</sup> and r are as defined above, and especially preferred from the group consisting of formulae VIIIc and VIId,



VIIIc



VIId

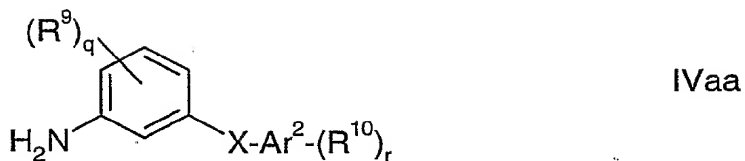
20 wherein R<sup>10</sup> and r are as defined above, or the alkaline metal salts and especially the sodium or potassium salts thereof.

Accordingly, in formulae IVa, VIII, VIIIa, VIIIb and IX, the bridging group X is preferably O, S, OCH<sub>2</sub> and OCH<sub>2</sub>CH<sub>2</sub> and especially is O.

25 In the formulae VIII, VIIIa and VIIIb, L<sup>8</sup> is preferably H or selected from the group consisting of Na, K and Cs and especially preferred is H.

In general, this reaction is advantageous to produce compounds of formula IVaa,

30



5

wherein  $R^9$ ,  $q$ ,  $X$ ,  $Ar^2$ ,  $R^{10}$  and  $r$  are as defined above/below.

To obtain compounds of formula IVaa, it is reasonable to employ a compound of formula VII that is selected from the compounds of formula VIIa,

10

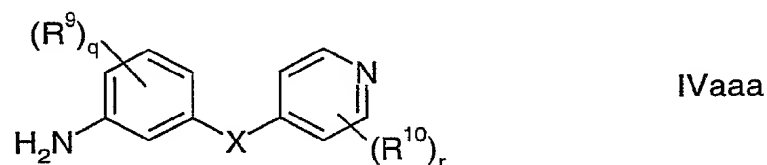


15

and proceed the reaction as described above/below.

Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIIa, the reaction preferably leads to compounds of formula IVaaa,

20

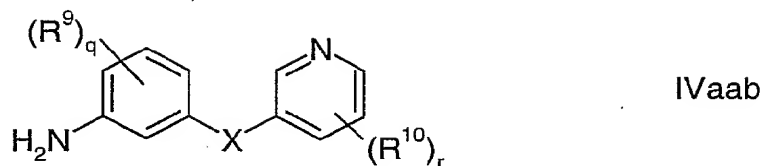


25

wherein  $R^9$ ,  $q$ ,  $X$ ,  $R^{10}$  and  $r$  are as defined above/below.

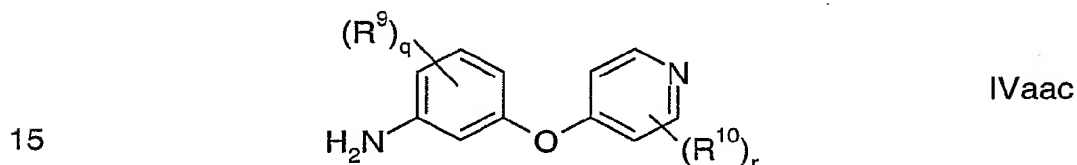
Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIIb, the reaction preferably leads to compounds of formula IVaab,

30



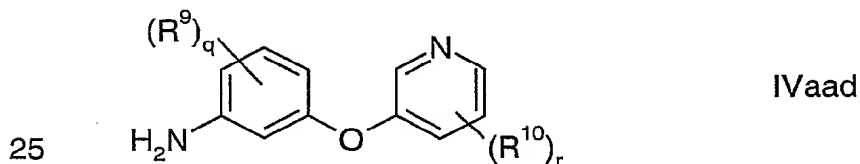
wherein  $R^9$ ,  $q$ ,  $X$ ,  $R^{10}$  and  $r$  are as defined above/below.

10 Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIIc, the reaction preferably leads to compounds of formula IVaac,



wherein  $R^9$ ,  $q$ ,  $R^{10}$  and  $r$  are as defined above/below.

20 Accordingly, by starting from a compound of formula VIIa and a compound of formula VIId, the reaction preferably leads to compounds of formula



wherein  $R^9$ ,  $q$ ,  $R^{10}$  and  $r$  are as defined above/below.

30 Some of the starting materials of the formula VII and/or the formula VIII are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

- The reaction between the compound of formula VII and VIII is preferably carried out in the temperature range between 0° and 250°, more preferred room temperature and 200°, for example at about 120°, at about 150° or at about 180°. Reaction times depend on the respective reactants and the respective reaction temperature, but generally lie in the range between 30 min and 36 hrs, preferably 3 hrs and 24 hrs, more preferably 8 hrs and 20 hrs for example about 10 hrs, about 16 hrs or about 18 hrs.
- The reaction can be carried out in the absence of solvent or preferably in the presence of an solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art. Examples for suitable solvents are high boiling aliphatic hydrocarbons, high boiling aromatic carbons, for example toluene, xylenes, high boiling chlorinated hydrocarbons, such as trichloroethylene, tetrachloroethanes, pentachloroethanes and hexachloroethanes; high boiling ethers, such as ethylene glycol and propylene glycols; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); sulfoxides, such as dimethyl sulfoxide (DMSO); or mixtures of the said solvents. Preferred are amides, especially dimethylformamide (DMF).
- Preferably, the reaction is carried out in the presence of a base. Suitable bases are known in the art. Preferred bases are organic bases and especially inorganic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Preferred inorganic bases are  $K_2CO_3$ ,  $Na_2CO_3$ ,  $MgCO_3$ ,  $CaCO_3$ , NaOH and KOH, especially preferred is  $K_2CO_3$ . Examples for organic

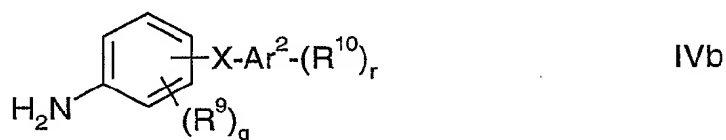
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bases are triethyl amine, diisopropyl ethyl amine (DIPEA), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction.

5

Alternatively, if the compound of formula IV is a compound according to formula IVb,

10



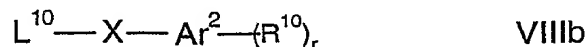
it can be readily obtained in an advantageous manner by reacting a compound of formula VIIb,

15



20 wherein  $R^9$  and  $q$  are as defined above/below and wherein  $L^9$  is selected independently from the meanings given for  $L^1$ . Preferably,  $L^9$  is halogen. More preferred,  $L^9$  is selected from the group consisting of Cl, Br and I. Especially preferred,  $L^9$  is Cl.

25 with a compound of formula VIIIb,



30

wherein  $L^{10}$  is H or a metal ion, preferably a metal ion, more preferred a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions, especially preferred alkaline



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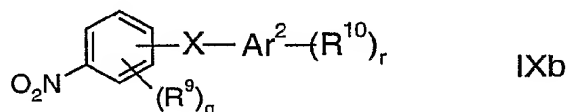
metal ions, of which Li, Na and K are especially preferred; and  $Ar^2$ ,  $R^{10}$ ,  $r$  and  $X$  are as defined above/below, and especially wherein  $X$  is  $(CHR^{11})_h$ - $Q$ - $(CHR^{12})_l$ ,  $CH=N-O$ ,  $CH=N-NR^{15}$ ,  $SO_2NR^{15}$ , wherein  $R^{15}$ ,  $R^{18}$  and  $R^{19}$  are as defined above/below;

5

optionally isolating the reaction product,

and transferring the obtained reaction product of formula IXb

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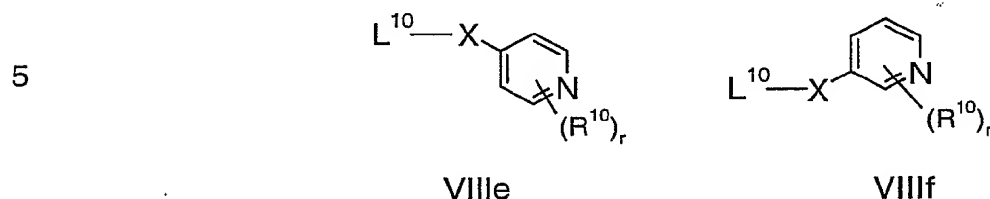


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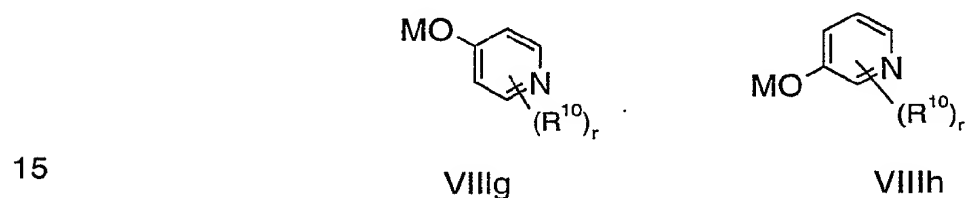
into a compound of formula Iva, preferably by hydrogenating the  $NO_2$ -moiety of the compound of formula IX into a  $NH_2$ -moiety. Methods and reaction conditions for hydrogenating said  $NO_2$ -moiety into a  $NH_2$ -moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, preferably a Palladium catalyst, for example Pd/C. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol, ethers, especially THF, and mixtures thereof. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between  $-20^\circ$  and  $150^\circ$ , preferably  $0^\circ$  and  $50^\circ$ .

30

Ar<sup>2</sup> is preferably pyridinyl. Accordingly, the compound of formula VIIIb is preferably selected from the group consisting of formulae VIIIe and VIIIf,



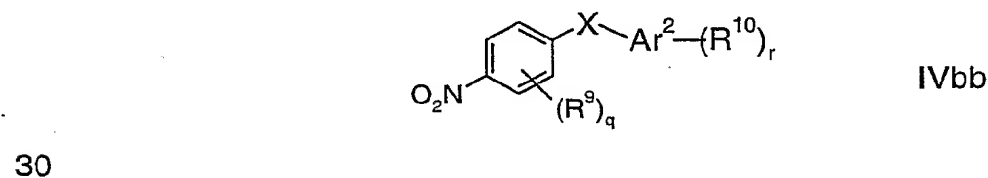
10 wherein L<sup>10</sup>, X, R<sup>10</sup> and r are as defined above, and especially preferred from the group consisting of formulae VIIIg and VIIIh,



20 wherein R<sup>10</sup> and r are as defined above, and wherein M is an alkaline metal ion and especially sodium or potassium, or the corresponding alcohols thereof.

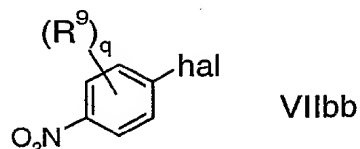
Accordingly, in formulae IVb, VIIIb, VIIIe, VIIIf and IXb, the bridging group X is preferably O, S, OCH<sub>2</sub> and OCH<sub>2</sub>CH<sub>2</sub> and especially is O.

25 In general, this alternative reaction is advantageous to produce compounds of formula IVbb,



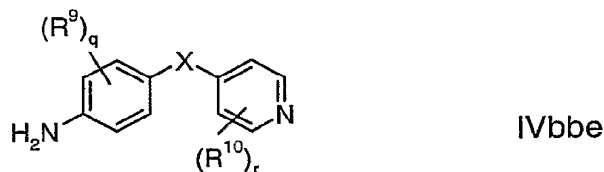
wherein R<sup>9</sup>, q, X, Ar<sup>2</sup>, R<sup>10</sup> and r are as defined above/below.

To obtain compounds of formula IVbb, it is reasonable to employ a compound of formula VIIb that is selected from the compounds of formula VIIbb,



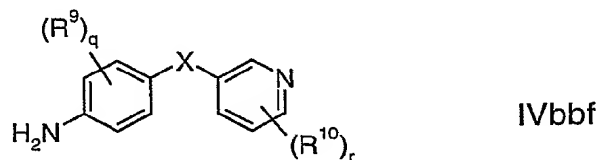
10 wherein hal is as defined above/below and especially is Cl, and proceed the alternative reaction as described above/below.

Accordingly, by starting from a compound a formula VIIbb and a compound of formula VIIe, the reaction preferably leads to compounds of formula IVbbe,



20 wherein  $R^9$ ,  $q$ ,  $X$ ,  $R^{10}$  and  $r$  are as defined above/below.

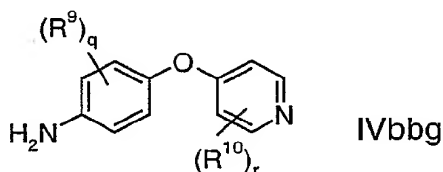
25 Accordingly, by starting from a compound of formula VIIbb and a compound of formula VIIIIf, the reaction preferably leads to compounds of formula IVbbf,



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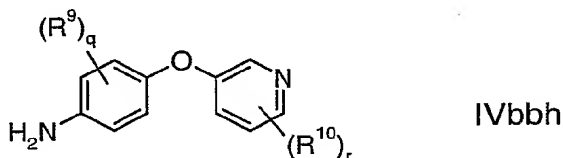
wherein  $R^9$ ,  $q$ ,  $X$ ,  $R^{10}$  and  $r$  are as defined above/below.

Accordingly, by starting from a compound of formula VIIbb and a  
 compound of formula VIIIg, the reaction preferably leads to compounds of  
 formula IVbbg,



wherein  $R^9$ ,  $q$ ,  $R^{10}$  and  $r$  are as defined above/below.

Accordingly, by starting from a compound of formula VIIb and a compound  
 of formula VIIIh, the reaction preferably leads to compounds of formula  
 IVbbh,



wherein  $R^9$ ,  $q$ ,  $R^{10}$  and  $r$  are as defined above/below.

Some of the starting materials of the formula VIIb and/or the formula VIIIb  
 are known and preferably commercially available. If they are not known,  
 they can be prepared by methods known per se.

The reaction between the compound of formula VIIb and VIIIb is preferably  
 carried out in the temperature range between  $0^\circ$  and  $250^\circ$ , more preferred  
 $50^\circ$  and  $220^\circ$ , for example at about  $90^\circ$ , at about  $120^\circ$ , at about  $160^\circ$ , at  
 about  $180^\circ$  or at about  $200^\circ$ . Reaction times depend on the respective  
 reactants and the respective reaction temperature, but generally lie in the

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range between 10 min and 24 hrs, preferably 30 min and 12 hrs, more preferably 1 h and 6 hrs for example about 1,5 hrs, about 3 hrs, about 4 hrs or about 5 hrs.

5 The reaction can be carried out in the absence or the presence of a solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art. Examples for suitable solvents are high aliphatic hydrocarbons, aromatic carbons, for example toluene and xylenes, high boiling  
10 chlorinated hydrocarbons, such as dichloromethane, trichloromethane trichloroethylene, tetrachloroethanes, pentachloroethanes and hexachloroethanes; ethers, such as diethylether, tert.-butyl methyl ether, ethylene glycol and propylene glycols; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether  
15 (diglyme); nitriles, such as acetonitrile, amides such as acetamide, diemthyacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); sulfoxides, such as dimethyl sulfoxide (DMSO); or mixtures of the said solvents.

20 Preferably, the reaction is carried out in the presence of a catalyst. Suitable catalysts are known in the art. Preferred catalytic active metals and especially copper.

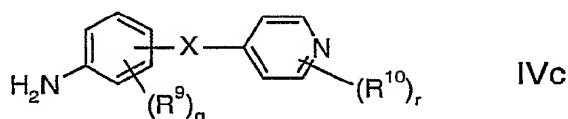
Preferably, the reaction is carried out by heating up a reaction mixture  
25 comprising one compound of formula VIIb and one compound of formula VIIIb to a suitable reaction temperature, which preferably lies at the upper end of the given temperature ranges and more preferred is in the range between 150° and 200°, for example at about 180°, preferably in the presence of the suitable catalyst and especially in the presence of copper.

30 Reaction times at this temperature are preferably as given above and especially in the range between 1 h and 5 hrs, for example about 3 hrs. Preferably, the reaction mixture is then allowed to cool down to a

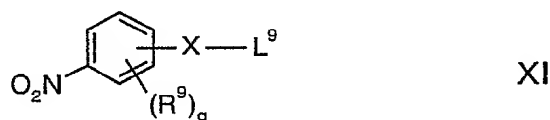
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temperature in the lower range of the given temperature, more preferred to a temperature in the range between 50° and 150°, for example to about 90°. Preferably, a suitable solvent, especially tert.-butyl methyl ether, is then added and the reaction mixture is preferably kept at about the same temperature for some more time, preferably for 30 min to 2 hrs and more preferred for about one hour.

If the compound IV is a compound according to formula IVc,

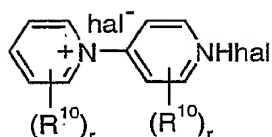


it can be readily obtained in an advantageous manner by reacting a compound of formula XI



- 20 wherein  $L^9$  is H or a metal ion, preferably a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred, and even more preferred is H; and  $R^9$ , q and X are as defined above/below, and especially wherein X is
- 25  $(CHR^{11})_h-Q-(CHR^{12})_l$ , wherein  $R^{11}$ , h and  $R^{12}$  are defined above/below, j is 0 and Q is selected from a group consisting of O, S,  $N-R^{15}$ ,  $(CHR^{18}-O)_j$ ,  $(CHR^{18}CHR^{19}-O)_j$ ,  $CH=N-O$ ,  $CH=N-NR^{15}$ ,  $SO_2NR^{15}$ , wherein  $R^{15}$ ,  $R^{18}$  and  $R^{19}$  are as defined above/below;
- 30 with a compound of formula XII,

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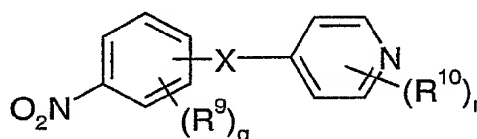


XII

5 wherein hal is independently select selected from the group consisting of Cl, Br and I, the residue  $R^{10}$  are the same or different and have the meanings given above/below and preferably have both the same meaning, and the indices  $r$  are the same or different and have the meanings given

10 above/below and preferably are the same,

optionally isolating the reaction product, and transferring the obtained reaction product of formula XIII



XIII

into a compound of formula IVc, preferably by hydrogenating the  $NO_2$ -moiety of the compound of formula XIII into a  $NH_2$ -moiety, for example as described above for the compound of formula IX.

20

In the compounds IVc, XII and XIII,  $r$  is preferably in each case identical and even more preferred in each case 0.

25

In formulae IVc, XI and XIII, the bridging group  $X$  is preferably O, S,  $OCH_2$  and  $OCH_2CH_2$  and especially is O.

In the formula XI,  $L^9$  is preferably H or selected from the group consisting of Na and K and especially preferred is H.

30

The reaction between the compound of formula XI and XII is preferably carried out in the temperature range between 0° and 250°, more preferred room temperature and 200°, for example at about 120°, at about 150° or at about 180°. Reaction times depend on the respective reactants and the  
 5 respective reaction temperature, but generally lie in the range between 30 min and 24 hrs, preferably one hour and 12 hrs, for example about 2 hrs, about 3 hrs or about 6 hrs. The reaction can be carried out in the absence of solvent or in the presence of an solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents  
 10 for carrying out the reaction are known in the art.

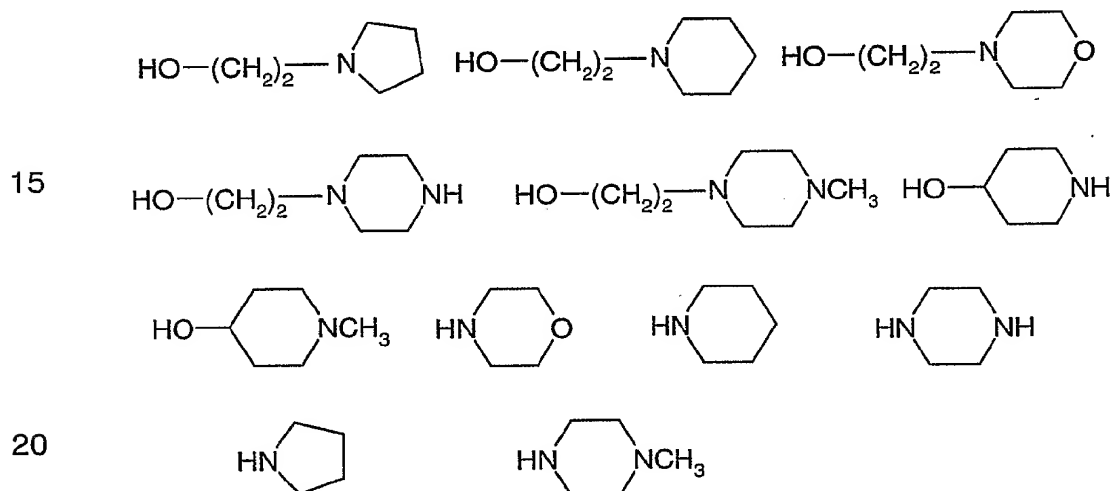
Some of the starting materials of the formula XI and/or the formula XII are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

15 Independently of the chosen reaction route, it is in many cases possible or even feasible to introduce residues  $R^8$ ,  $R^9$  and/or  $R^{10}$  into one or more of the compounds described above, or, if the compound already comprises one or more residues  $R^8$ ,  $R^9$  and/or  $R^{10}$ , to introduce additional residues  
 20  $R^8$ ,  $R^9$  and/or  $R^{10}$  into said compound. The introduction of additional residues can be readily performed by methods known in the art and especially by aromatic substitution, for example nucleophilic aromatic substitution or electrophilic aromatic substitution. For example, in compounds comprising  $Ar^1$ , wherein  $Ar^1$  comprises one or more halogen and preferably fluorine substituents, one or more of the halogen/fluorine  
 25 substituents can be easily substituted by hydroxy, thio and/or amino substituted hydrocarbons, preferably selected from the group consisting of  $HO(CH_2)_nNR^{11}R^{12}$ ,  $HO(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $HO(CH_2)_nNR^{11}(CH_2)_kOR^{12}$ ,  $HO(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$ ,  $HO(CH_2)_nCOOR^{13}$ ,  $HO(CH_2)_nS(O)_uR^{13}$   
 30  $HNR^{11}(CH_2)_nNR^{11}R^{12}$ ,  $HNR^{11}(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  $HNR^{11}(CH_2)_nNR^{11}(CH_2)_kOR^{12}$ ,  $HNR^{11}(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$ ,  $HNR^{11}(CH_2)_nCOOR^{12}$  and  $HNR^{11}(CH_2)_nS(O)_uR^{13}$  wherein  $R^{11}$ ,  $R^{12}$  and  $R^{13}$



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are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. In this embodiment  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. Even more preferred, the hydroxy, thio and/or amino substituted hydrocarbons are selected from the group consisting of  $NH_3$ ,  $HN(CH_3)_2$ ,  $NH_2CH_3$ ,  $HN(C_2H_5)_2$ ,  $H_2NCH_2CH_2NH_2$ ,  $HOCH_2CH_2NH_2$ ,  $HOCH_2CH_2NHCH_3$ ,  $HN(CH_3)CH_2CH_2NH_2$ ,  $HN(CH_3)CH_2CH_2N(CH_3)_2$ ,  $HN(CH_3)CH_2CH_2N(CH_3)_2$ ,  $HN(CH_3)CH_2CH_2OCH_3$ ,  $HOCH_2CH_2N(CH_3)_2$ ,  $HOCH_2CH_2N(CH_2CH_3)_2$ ,  $HSCH_3$ ,  $HSC_2H_5$ , and compounds of the formulae



or salts and especially metal salts thereof.

On the other hand, it is in many cases possible or even feasible to modify or derivatize one or more of the residue is  $R^8$ ,  $R^9$  and  $R^{10}$  into residues  $R^8$ ,  $R^9$  and/or  $R^{10}$  other than the ones originally present. For example,  $CH_3$ -groups can be oxidized into aldehyde groups or carbonic acid groups, thio atom containing groups, for example S-alkyl or S-aryl groups, can be oxidized into  $SO_2$ -alkyl or  $SO_2$ -aryl groups, respectively, carboxylic acid groups can be derivatized to carboxylic acid ester groups or carboxylic acid amide groups and carboxylic acid ester groups or carboxylic acid amide

groups can be hydrolysed into the corresponding carboxylic acid groups. Methods for performing such modifications or derivatizations are known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

- 5 Every reaction step described herein can optionally be followed by one or more working up procedures and/or isolating procedures. Suitable such procedures are known in the art, for example from standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart). Examples for such
- 10 procedures include, but are not limited to evaporating a solvent, distilling, crystallization, fractionised crystallization, extraction procedures, washing procedures, digesting, filtration procedures, chromatography and chromatography by HPLC.
- 15 A base of the formula I or the formula II can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in a preferably inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it
- 20 is possible to use inorganic acids, for example sulfuric acid, sulfurous acid, dithionic acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as, for example, orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic
- 25 monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, hexanoic acid, octanoic acid, decanoic acid, hexadecanoic acid, octadecanoic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid,
- 30 ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, trimethoxybenzoic acid, adamantanecarboxylic acid, p-toluene-

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sulfonic acid, glycolic acid, embonic acid, chlorophenoxyacetic acid, aspartic acid, glutamic acid, proline, glyoxylic acid, palmitic acid, parachlorophenoxyisobutyric acid, cyclohexanecarboxylic acid, glucose 1-phosphate, naphthalenemono- and -disulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I. On the other hand, compounds of the formula I can be converted into the corresponding metal salts, in particular alkali metal salts or alkaline earth metal salts, or into the corresponding ammonium salts, using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Suitable salts are furthermore substituted ammonium salts, for example the dimethyl-, diethyl- and diisopropyl-ammonium salts, monoethanol-, diethanol- and diisopropanolammonium salts, cyclohexyl- and dicyclohexylammonium salts, dibenzylethylenedi-ammonium salts, furthermore, for example, salts with arginine or lysine.

On the other hand, if desired, the free bases of the formula I or the formula II can be liberated from their salts using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).

The invention relates to compounds of the formula I and of the formula II and physiologically acceptable salts and solvates thereof as medicaments.

The invention also relates to the compounds for the formula I and of the formula II and physiologically acceptable salts and solvates thereof as kinase inhibitors.

The invention furthermore relates to the use of the compounds of the formula I and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non-chemical methods. The invention

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furthermore relates to the use of the compounds of the formula II and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non-chemical methods. In this cases, one or more

5 compounds according to the invention can be converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

10 The invention further relates to the use of one or more of the compounds according to the invention, selected from the group consisting of compounds of the formula I as free bases, solvates of compounds of the formula I, salts of compounds of formula I, of compounds of the formula II as free bases, solvates of compounds of the formula II and salts of

15 compounds of formula II, for the production of pharmaceutical compositions and/or pharmaceutical preparations, in particular by a non-chemical route. In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art

20 that transfer one or more compounds according to the invention into a dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more compounds according to the invention into such a dosage form comprises the addition of one or more compounds, selected from the group consisting of carriers,

25 excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to the invention. Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingredients. In this respect, active ingredients are

30 preferably at least one compound according to this invention and one or more additional compounds other than the compounds according to the invention, which show valuable pharmaceutical properties, preferably

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those pharmaceutical active agents other than the compounds according to invention which are disclosed herein.

5 The process for preparing pharmaceutical compositions and/or pharmaceutical preparations preferably comprises one or more processing steps, selected from the group consisting of combining, milling, mixing, granulating, dissolving, dispersing, homogenizing and compressing. The one or more processing steps are preferably performed on one or more of the ingredients which are to form the pharmaceutical composition and/or  
10 pharmaceutical preparation preferably according to invention. Even more preferred, said processing steps are performed on two or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation, said ingredients comprising one or more compounds according to the invention and, additionally, one or more  
15 compounds, preferably selected from the group consisting of active ingredients other than the compounds according to the invention, excipients, auxiliaries, adjuvants and carriers. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition.

20 Preferably, one or more compounds according to the invention are converted into a suitable dosage form together with at least one compound selected from the group consisting of excipients, auxiliaries, adjuvants and carriers, especially solid, liquid and/or semi-liquid excipients, auxiliaries,  
25 adjuvants and carriers, and, if desired, in combination with one or more further active ingredients.

Suitable dosage forms include, but are not limited to tablets, capsules, semi-solids, suppositories, aerosols, which can be produced according to  
30 methods known in the art, for example as described below:

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- 5                    tablets                    mixing of active ingredient/s and auxiliaries,  
compression of said mixture into tablets  
(direct compression), optionally granulation  
of part of mixture before compression
- 10                   capsules                    mixing of active ingredient/s and auxiliaries  
to obtain a flowable powder, optionally  
granulating powder, filling  
powders/granulate into opened capsules,  
capping of capsules
- 15                   semi-solids (ointments, gels, creams)                    dissolving/dispersing active  
ingredient/s in an aqueous or fatty carrier;  
subsequent mixing of aqueous/fatty phase  
with complementary fatty resp. aqueous  
phase, homogenisation (creams only)
- 20                   suppositories (rectal and vaginal)                    dissolving/dispersing active ingredient/s  
in carrier material liquified by heat (rectal:  
carrier material normally a wax; vaginal:  
carrier normally a heated solution of a  
gelling agent), casting said mixture into  
suppository forms, annealing and  
withdrawal suppositories from the forms
- 25                   aerosols:                    dispersing/dissolving active agent/s in a  
propellant, bottling said mixture into an  
atomizer

30                   The invention thus relates to pharmaceutical compositions and/or  
pharmaceutical preparations comprising at least one compound of the  
formula I and/or one of its physiologically acceptable salts and/or solvates  
and especially to pharmaceutical compositions and/or pharmaceutical

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preparations comprising at least one compound of the formula II and/or one of its physiologically acceptable salts and/or solvates.

5 Preferably, the pharmaceutical compositions and/or pharmaceutical preparations according to the invention contain a therapeutic effective amount of one or more compounds according to the invention. Said therapeutic effective amount of one or more of the compounds according to the invention is known to the skilled artisan or can be easily determined by standard methods known in the art. For example, the compounds  
10 according to the invention can be administered to a patient in an analogous manner to other compounds that are effective as raf-kinase inhibitors. Usually, suitable doses that are therapeutically effective lie in the range between 0.0005 mg and 1000 mg, preferably between 0.005 mg and 500 mg and especially between 0.5 and 100 mg per dose unit. The  
15 daily dose comprises preferably more than 0.001 mg, more preferred more than 0.01 milligram, even more preferred more than 0.1 mg and especially more than 1.0 mg, for example more than 2.0 mg, more than 5 mg, more than 10 mg, more than 20 mg, more than 50 mg or more than 100 mg, and preferably less than 1500 mg, more preferred less than 750 mg, even  
20 more preferred less than 500 mg, for example less than 400 mg, less than 250 mg, less than 150 mg, less than 100 mg, less than 50 mg or less than 10 mg.

The specific dose for the individual patient depends, however, on the  
25 multitude of factors, for example on the efficacy of the specific compounds employed, on the age, body weight, general state of health, the sex, the kind of diet, on the time and route of administration, on the excretion rate, the kind of administration and the dosage form to be administered, the pharmaceutical combination and severity of the particular disorder to which  
30 the therapy relates. The specific therapeutic effective dose for the individual patient can readily be determined by routine experimentation, for

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example by the doctor or physician which advises or attends the therapeutic treatment.

5 However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the rate of excretion, medicament combination and severity of the particular illness to which the therapy applies. Parenteral administration is preferred. Oral administration is  
10 especially preferred.

These compositions and/or preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or  
15 topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or vaseline. Examples for suitable dosage forms, which are especially suitable for oral administration  
20 are, in particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops. Further examples for suitable dosage forms, which are especially suitable for rectal administration are suppositories, further examples for suitable dosage forms, which are especially suitable for parenteral administration are solutions, preferably  
25 oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The compositions and/or preparations indicated may be  
30 sterilized and/or comprise assistants, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for modifying the



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osmotic pressure, buffer substances, dyes and flavors and/or one or more further active ingredients, for example one or more vitamins.

5 For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO<sub>2</sub> or chlorofluorocarbons). The active ingredient is advantageously used here in micronized form, in which case one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered  
10 with the aid of conventional inhalers.

The compounds of the formula I and their physiologically acceptable salts and solvates and especially the compounds of formula II and their physiologically acceptable salts and solvates can be employed for  
15 combating one or more diseases, for example allergic diseases, psoriasis and other skin diseases, especially melanoma, autoimmune diseases, such as, for example, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus or ulcerative colitis.

20 In general, the substances according to the invention are preferably administered in doses corresponding to the compound rolipram of between 1 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of  
25 factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination and severity of the particular illness to which the therapy applies.

30 The compounds of the formula I according to claim 1 and/or their physiologically acceptable salts are also used in pathological processes

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which are maintained or propagated by angiogenesis, in particular in tumours, restenoses, diabetic retinopathy, macular degenerative disease or rheumatoid arthritis.

5 Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety  
10 of means. A preferred means is to measure the physiological potency of a given compound.

For use in the subject methods, the subject compounds may be formulated with pharmaceutically active agents other than the compounds according  
15 to the invention, particularly other anti-metastatic, antitumor or anti-angiogenic agents. Angiostatic compounds of interest include angiostatin, enclostatin, carboxy terminal peptides of collagen alpha (XV), etc. Cytotoxic and cytostatic agents of interest include adriamycin, aleran, Ara-C, BICNU, busulfan, CNNU, cisplatin, cytoxan, daunorubicin, DTIC, 5-  
20 FU, hydrea, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen mustard, velban, vincristine, vinblastine, VP-16, carboplatin, fludarabine, gemcitabine, idarubicin, irinotecan, leustatin, navelbine, taxol, taxotere, topotecan, etc.

25 The compounds of the invention preferably show antiproliferative effects, for example in an in vivo xenograft tumor model. The subject compounds can be administered to a subject having a hyperproliferative disorders, e.g., to inhibit tumor growth, to decrease inflammation associated with a lymphoproliferative disorder, to inhibit graft rejection, or neurological  
30 damage due to tissue repair, etc. The present compounds can be useful for prophylactic or therapeutic purposes. As used herein, the term "treating" is used to refer to both prevention of disease, and treatment of

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pre-existing conditions. The prevention of proliferation is accomplished by administration of the subject compounds prior to development of overt disease, e.g., to prevent the regrowth of tumors, prevent metastatic growth, diminish restenosis associated with cardiovascular surgery, etc.

5 Alternatively the compounds are used to treat ongoing disease, by stabilizing or improving the clinical symptoms of the patient.

Furthermore, the compounds according the invention preferably can be utilized in the treatment of infectious diseases of diverse genesis.

10

Infections according the invention include, but are not limited to infections caused by pathogenic microorganisms, such as bacteria, fungi, viruses and protozoans, for example influenza (Pleschka, S. et al. Nature Cell Biol. 2001, 3, page 301-305), retroviruses, for example HIV infection (Yang, X. et al. J. Biol. Chem. 1999, 274, page 27981-27988; Popik, W et al Mol Cel Biol. 1996, 16, page 6532-6541), Hepatitis B (Benn, J et al., Proc. Natl. Acad. Sci. 1995, 92, page 11215-11219), Hepatitis C (Aoki et al. J. Virol. 2000, 74, page 1736-1741), papillomavirus, parainfluenza, rhinoviruses, adenoviruses, Helicobacter pylori, and viral and bacterial infections of the skin (e.g. cold sores, warts, chickenpox, molluscum. contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, Athlete's foot and ringworm).

15

20

Furthermore, the compounds according the invention preferably show anti-angiogenic properties.

25

Thus, compounds of the present invention can be advantageously employed in the treatment of one or more diseases afflicting mammals which are characterized by cellular proliferation in the area of disorders associated with neo-vascularization and/or vascular permeability including blood vessel proliferative disorders including arthritis and restenosis; fibrotic disorders including hepatic cirrhosis and atherosclerosis; mesangial

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cell proliferative disorders include glomerulonephritis, diabetic  
nephropathy, malignant nephrosclerosis, thrombotic microangiopathy  
syndromes, organ transplant rejection and glomerulopathies; and  
metabolic disorders include psoriasis, diabetes mellitus, chronic wound  
5 healing, inflammation and neurodegenerative diseases.

The host, or patient, may be from any mammalian species, e.g., primate  
sp., particularly human; rodents, including mice, rats and hamsters;  
rabbits; equines, bovines, canines, felines; etc. Animal models are of  
10 interest for experimental investigations, providing a model for treatment of  
human disease.

The susceptibility of a particular cell to treatment with the subject  
compounds may be determined by in vitro testing. Such in vitro testing  
15 methods are known in the art. For example, they can be performed as  
described herein or in the literature cited herein, or in an analogous  
manner thereof. Typically a culture of the cell is combined with a subject  
compound at varying concentrations for a period of time sufficient to allow  
the active agents to induce cell death or inhibit migration, usually between  
20 about one hour and one week. For in vitro testing, cultured cells from a  
biopsy sample may be used. The viable cells left after treatment are then  
counted.

The dose will vary depending on the specific compound utilized, specific  
25 disorder, patient status, etc. Typically a therapeutic dose will be sufficient  
to substantially decrease the undesirable cell population in the targeted  
tissue, while maintaining patient viability. Treatment will generally be  
continued until there is a substantial reduction, e.g., at least about 50 %,  
decrease in the cell burden, and may be continued until there are  
30 essentially none of the undesirable cells detected in the body.

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The compounds according to the invention are preferably administered to human or nonhuman animals, more preferred to mammalian animals and especially to humans.

- 5 The compounds also find use in the specific inhibition of a signaling pathway mediated by protein kinases. Protein kinases are involved in signaling pathways for such important cellular activities as responses to extracellular signals and cell cycle checkpoints. Inhibition of specific protein kinases provided a means of intervening in these signaling
- 10 pathways, for example to block the effect of an extracellular signal, to release a cell from cell cycle checkpoint, etc. Defects in the activity of protein kinases are associated with a variety of pathological or clinical conditions, where there is a defect in the signaling mediated by protein kinases. Such conditions include those associated with defects in cell cycle
- 15 regulation or in response to extracellular signals, e.g., immunological disorders, autoimmune and immunodeficiency diseases; hyperproliferative disorders, which may include infection, psoriasis, arthritis, inflammation, endometriosis, scarring, cancer, etc. The compounds of the present invention are active in inhibiting purified kinase proteins preferably raf
- 20 kinases, e.g., there is a decrease in the phosphorylation of a specific substrate in the presence of the compound. The compounds of the invention may also be useful as reagents for studying signal transduction or any of the clinical disorders listed throughout this application.
- 25 There are many disorders associated with a dysregulation of cellular proliferation. The conditions of interest include, but are not limited to, the following conditions. The subject compounds are useful in the treatment of a variety of conditions where there is proliferation and/or migration of smooth muscle cells, and/or inflammatory cells into the intimal layer of a
- 30 vessel, resulting in restricted blood flow through that vessel, e.g., neointimal occlusive lesions. Occlusive vascular conditions of interest include atherosclerosis, graft coronary vascular disease after

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transplantation, vein graft stenosis, peri-anastomatic prothetic graft stenosis, restenosis after angioplasty or stent placement, and the like.

5 Diseases where there is hyperproliferation and tissue remodelling or repair or reproductive tissue, e.g., uterine, testicular and ovarian carcinomas, endometriosis, squamous and glandular epithelial carcinomas of the cervix, etc. are reduced in cell number by administration of the subject compounds. The growth and proliferation of neural cells is also of interest.

10 Tumor cells are characterized by uncontrolled growth, invasion to surrounding tissues, and metastatic spread to distant sites. Growth and expansion requires an ability not only to proliferate, but also to down-modulate cell death (apoptosis) and activate angiogenesis to produce a tumor neovasculature.

15 Tumors of interest for treatment include carcinomas, e.g., colon, duodenal, prostate, breast, melanoma, ductal, hepatic, pancreatic, renal, endometrial, stomach, dysplastic oral mucosa, polyposis, invasive oral cancer, non-small cell lung carcinoma, transitional and squamous cell  
20 urinary carcinoma etc.; neurological malignancies; e.g. neuroblastoma, gliomas, etc.; hematological malignancies, e.g., childhood acute leukaemia, non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, malignant cutaneous T-cells, mycosis fungoides, non-MF cutaneous T-cell-lymphoma, lymphomatoid papulosis, T-cell rich cutaneous lymphoid  
25 hyperplasia, bullous pemphigoid, discoid lupus erythematosus, lichen planus, etc.; and the like.

30 Tumors of neural tissue are of particular interest, e.g., gliomas, neuromas, etc. Some cancers of particular interest include breast cancers, which are primarily adenocarcinoma subtypes. Ductal carcinoma in situ is the most common type of noninvasive breast cancer. In DCIS, the malignant cells have not metastasized through the walls of the ducts into the fatty tissue of

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the breast. Infiltration (or invasive) ductal carcinoma (IDC) has metastasized through the wall of the duct and invaded the fatty tissue of the breast. Infiltrating (or invasive) lobular carcinoma (ILC) is similar to IDC, in that it has the potential to metastasize elsewhere in the body.

5 About 10 % to 15 % of invasive breast cancers are invasive lobular carcinomas.

Also of interest is non-small cell lung carcinoma. Non-small cell lung cancer (NSCLC) is made up of three general subtypes of lung cancer.

10 Epidermoid carcinoma (also called squamous cell carcinoma) usually starts in one of the larger bronchial tubes and grows relatively slowly. The size of these tumors can range from very small to quite large. Adenocarcinoma starts growing near the outside surface of the lung and may vary in both size and growth rate. Some slowly growing adenocarcinomas are

15 described as alveolar cell cancer. Large cell carcinoma starts near the surface of the lung, grows rapidly, and the growth is usually fairly large when diagnosed. Other less common forms of lung cancer are carcinoid, cylindroma, mucoepidermoid, and malignant mesothelioma.

20 Melanoma is a malignant tumor of melanocytes. Although most melanomas arise in the skin, they also may arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma occurs predominantly in adults, and more than half of the cases arise in apparently normal areas of the skin. Prognosis is affected by clinical and

25 histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, tumor infiltrating lymphocytes, and ulceration or bleeding at the primary site affect the prognosis. Clinical staging is based on whether the tumor has spread to regional lymph nodes or distant sites. For disease clinically confined to the

30 primary site, the greater the thickness and depth of local invasion of the melanoma, the higher the chance of lymph node metastases and the worse the prognosis. Melanoma can spread by local extension (through

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lymphatics) and/or by hematogenous routes to distant sites. Any organ may be involved by metastases, but lungs and liver are common sites.

Other hyperproliferative diseases of interest relate to epidermal hyperproliferation, tissue, remodeling and repair. For example, the chronic skin inflammation of psoriasis is associated with hyperplastic epidermal keratinocytes as well as infiltrating mononuclear cells, including CD4+ memory T cells, neutrophils and macrophages.

The proliferation of immune cells is associated with a number of autoimmune and lymphoproliferative disorders. Diseases of interest include multiple sclerosis, rheumatoid arthritis and insulin dependent diabetes mellitus. Evidence suggests that abnormalities in apoptosis play a part in the pathogenesis of systemic lupus erythematosus (SLE). Other lymphoproliferative conditions the inherited disorder of lymphocyte apoptosis, which is an autoimmune lymphoproliferative syndrome, as well as a number of leukemia's and lymphomas. Symptoms of allergies to environmental and food agents, as well as inflammatory bowel disease, may also be alleviated by the compounds of the invention.

Surprisingly, it has been found that glycine amide derivatives according to invention are able to interact with signaling pathways, especially the signaling pathways described herein and preferably the raf-kinase signaling pathway. Glycine amide derivatives according to the invention preferably show advantageous biological activity which can easily be demonstrated according to methods known in the art, for example by enzyme based assays. Suitable assays are known in the art, for example from the literature cited herein and the references cited in the literature, or can be developed and/or performed in an analogous manner thereof. In such enzyme based assays, glycine amide derivatives according to invention show an effect, preferably a modulating and especially an inhibiting effect which is usually documented by  $IC_{50}$  values in a suitable



range, preferably in the micromolar range and more preferred in the nanomolar range.

5 In general, compounds according to the invention are to be regarded as suitable kinase-modulators and especially suitable kinase-inhibitors according to the invention if they show an effect or an activity to one or more kinases, preferably to one or more raf-kinases that preferably lies, determined as  $IC_{50}$ -value, in the range of 100  $\mu$ mol or below, preferably 10  $\mu$ mol or below, more preferably in the range of 3  $\mu$ mol or below, even more  
10 preferably in the range of 1  $\mu$ mol or below and most preferably in the nanomolar range. Especially preferred for use according to the invention are kinase-inhibitors as defined above/below, that show an activity, determined as  $IC_{50}$ -value, to one or more raf-kinases, preferably including A-raf, B-raf and c-raf1 or consisting of A-raf, B-raf and c-raf1 and more  
15 preferred including c-raf1 or consisting of c-raf1, in the range of 0.5  $\mu$ mol or below and especially in the range of 0.1  $\mu$ mol or below. In many cases an  $IC_{50}$ -value at the lower end of the given ranges is advantageous and in some cases it is highly desirable that the  $IC_{50}$ -value is as small as possible or the  $IC_{50}$ -values are as small as possible, but in general  $IC_{50}$ -values  
20 that lie between the above given upper limits and a lower limit in the range of 0.0001  $\mu$ mol, 0.001  $\mu$ mol, 0.01  $\mu$ mol or even above 0.1  $\mu$ mol are sufficient to indicate the desired pharmaceutical activity. However, the activities measured can vary depending on the respective testing system or assay chosen.

25 As discussed herein, these signaling pathways are relevant for various disorders. Accordingly, by interacting with one or more of said signaling pathways, glycine amide derivatives are useful in the prevention and/or the treatment of disorders that are dependent from said signaling pathways.

30 Subject of the present invention are therefore glycine amide derivatives according to the invention as promoters or inhibitors, preferably as

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inhibitors, of the signaling pathways described herein. Preferred subject of the invention are therefore glycine amide derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of the raf-kinase pathway. More preferred subject of the invention are therefore  
5 glycine amide derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of the raf-kinase. Even more preferred subject of the invention are glycine amide derivatives according to invention as promoters or inhibitors, preferably as inhibitors, of one or more raf-kinases, selected from the group consisting of A-raf, B-raf and c-  
10 raf1. Especially preferred subject of the invention are glycine amide derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of c-raf1.

Thus, subject of the present invention are glycine amide derivatives  
15 according to the invention as medicaments. Subject of the present invention are glycine amide derivatives according to the invention as medicament active ingredients. Further subject of the present invention is the use of one or more glycine amide derivatives according to the invention as a pharmaceutical. Further subject of the present invention is the use of  
20 one or more glycine amide derivatives according to the invention in the treatment and/or the prophylaxis of disorders, preferably the disorders described herein, more preferred disorders that are caused, mediated and/or propagated by signalling pathways discussed herein, even more preferred disorders that are caused, mediated and/or propagated by raf-  
25 kinases and especially disorders that are caused, mediated and/or propagated by raf-kinases, selected from the group consisting of A-raf, B-raf and c-raf1. Usually, the disorders discussed herein are divided into two groups, hyperproliferative and non hyperproliferative disorders. In this context, infection, psoriasis, arthritis, inflammation, endometriosis,  
30 scarring, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases are to be regarded as noncancerous disorders, of which infections, arthritis, inflammation,

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immunological diseases, autoimmune diseases and immunodeficiency diseases are usually regarded as non hyperproliferative disorders. In this context, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia are to be regarded as cancerous disorders, all of which are usually regarded as hyperproliferative disorders. Especially cancerous cell growth and especially cancerous cell growth mediated by raf-kinase is a disorder which is a target of the present invention. Subject of the present invention therefore are glycine amide derivatives according to the invention as medicaments and/or medicament active ingredients in the treatment and/or the prophylaxis of said disorders and the use of glycine amide derivatives according to the invention for the manufacture of a pharmaceutical for the treatment and/or the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising administering one or more glycine amide derivatives according to the invention to a patient in need of such an administration.

Accordingly, subject of the present invention are pharmaceutical compositions that contain one or more glycine amide derivatives according to the invention. Subject of the present invention are especially pharmaceutical compositions that contain one or more glycine amide derivatives according to the invention and one or more additional compounds (other than the compounds of the instant invention), preferably selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutically active ingredients other than the compounds according to the invention.

Accordingly, subject of the present invention is a process for the manufacture of a pharmaceutical composition, wherein one or more glycine amide derivatives according to the invention and one or more compounds (other than the compounds of the instant invention), preferably selected from the group consisting of carriers, excipients, auxiliaries,

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adjuvants and pharmaceutically active ingredients other than the compounds according to the invention.

5 Accordingly, the use of the compounds according to the invention in the treatment of hyperproliferative disorders is a subject of the instant invention.

10 Accordingly, the use of the compounds according to the invention for producing a medicament for the treatment of hyperproliferative disorders is a subject of the instant invention.

Above and below, all temperatures are given in °C. In the examples below, "conventional work-up" means that the organic phase is washed with saturated NaHCO<sub>3</sub> solution, if desired with water and saturated NaCl solution, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel, by preparative HPLC and/or by crystallization.

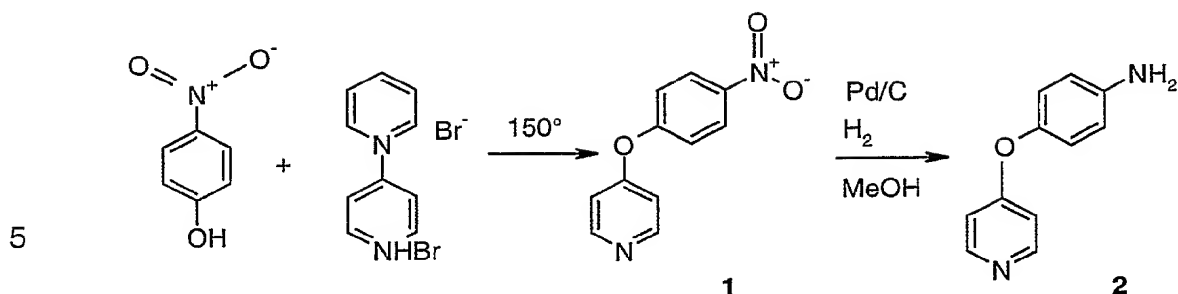
20 The present invention relates to glycinamide derivatives of formula I, the use of the compounds of formula I as inhibitors of raf-kinase, the use of the compounds of formula I for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient.

## 25 Examples

4-(4-Pyridinyloxy)-phenylamine (2)

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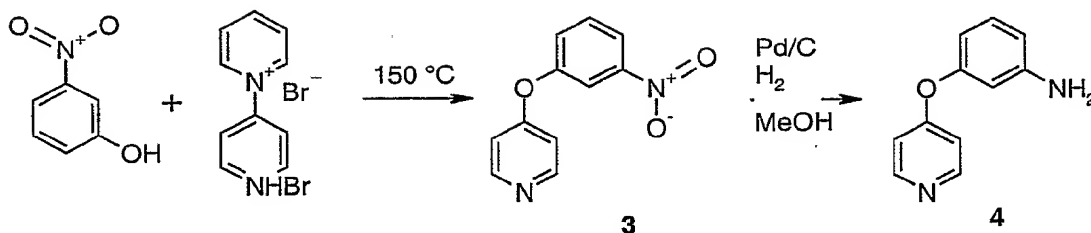
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- a) In a reaction apparatus equipped with a stirring means and a cooler, 195 g (1.4 mol) 4-nitrophenol and 445.2 g (1.4 mol) bipyridin are slowly heated up to a temperature of 150 °C under agitation. After three hours of stirring at 150 °C, the hot reaction mixture is poured into ice-cool water, acidified with hydrochloric acid and washed with methyl tert.-butyl ether (2 x 3 l). The organic phase is turned basic (pH about 12) by addition of concentrated caustic soda solution and extracted with methyl tert.-butyl ether (2 x 3 l). The combined organic phases are washed with water (4 x 1 l), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The residue is dissolved in 100 ml ether, cooled in an ice bath and caused to crystallize by addition of petroleum ether (200 ml). The crystalline residue is collected by suction and dried in vacuum to yield 75 g (25 %) brownish crystals of 1.
- b) Compound 1 is hydrogenated with Pd/C in methanol. The reaction mixture is filtered over kieselguhr, the residue washed with methanol and the filtrate evaporated. The residue is digested with a diethyl ether/petroleum ether-mixture (2:1), filtered by suction, washed with petrol ether and dried in vacuo at 40 °C overnight to yield 50.94 g (76 %) brownish crystals of 2.

3-(4-Pyridinyloxy)-phenylamine (4)

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a) In a reaction apparatus equipped with a stirring means and a cooler, 200 g (1.44 mol/l) 3-nitrophenol and 457.93 g (1.44 mol) bipyridin are slowly heated up to a temperature of 150 °C under agitation. After three hours of stirring at 150 °C, the hot reaction mixture is poured into ice-cool water, acidified with hydrochloric acid and washed with methyl tert.-butyl ether (2 x 3 l). The organic phase is turned basic (pH about 12) by addition of concentrated caustic soda solution and extracted with methyl tert.-butyl ether (2 x 3 l). The combined organic phases are washed with water (4 x 1 l), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The residue is dissolved in 200 ml diethyl ether, treated with charcoal (20 g) for 1 h under stirring and filtered. The filtrate is evaporated to about 200 ml, cooled in a ice bath and caused to crystallize by addition of petroleum ether (500 ml). The crystalline residue is collected by suction and dried in vacuum to yield 131 g (42 %) light brownish crystals of 3.

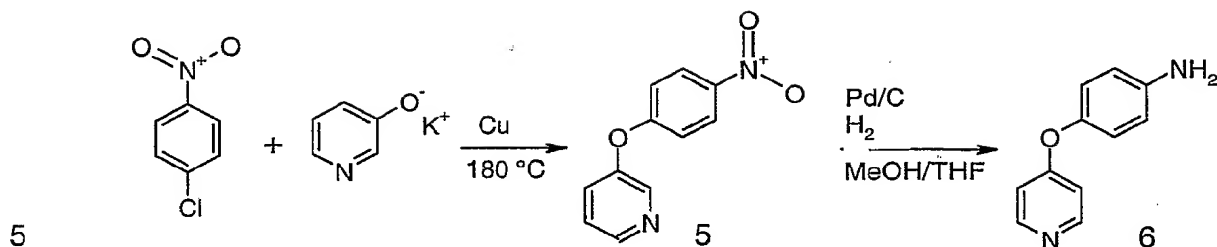
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b) Compound 3 is hydrogenated with Pd/C in methanol. The reaction mixture is filtered over kieselguhr, the residue washed with methanol and the filtrate evaporated. The residue is digested with diethyl ether, filtered by suction, washed with diethyl ether and dried in vacuum at 40 °C overnight to yield 98.08 g (87 %) light brownish crystals of 4.

4-(3-Pyridinyloxy)-phenylamine (6)

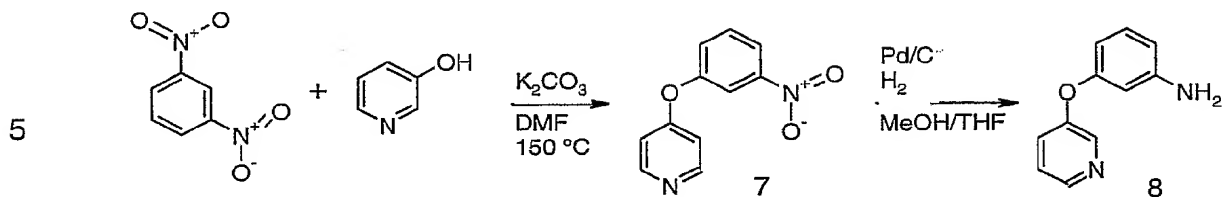
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- a) In a reaction apparatus equipped with a stirring means and a cooler, 125 g (0.94 mol) 3-hydroxypyridine, potassium salt, 300 g 1-chloronitrobenzene and 15 g copper are heated up to a temperature of 180 °C under agitation for homogenization. After three hours of stirring at 180 °C, the reaction mixture is cooled to 90 °C and methyl-tert.-butyl ether is added quickly. The resulting suspension is further stirred for 1 h, filtered by suction and the filtrate is extracted with 10 % aqueous hydrochloric acid (3 x 1 l). The resulting aqueous phase is made alkaline with ammonium hydroxide solution and extracted with ethyl acetate. The obtained organic phase is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated in vacuum. The residue is purified by column chromatography on silica gel (1 kg) with dichloromethane as eluent, dissolved in 10 % aqueous hydrochloric acid and extracted with ethyl acetate. The aqueous phase is made alkaline with ammonium hydroxide solution and the resulting crystalline precipitate is collected by suction, washed with little cold water and dried on air for 4 days to yield 44.7 g (22 %) brownish crystals of 5.
- b) Compound 5 is hydrogenated with Pd/C in methanol/tetrahydrofuran at room temperature. The reaction mixture is filtered over kieselguhr, the residue washed with methanol and the filtrate evaporated. The residue is digested with diethyl ether, filtered by suction, washed with diethyl ether and dried in vacuum at 40 °C overnight to yield 37.14 g (95 %) light brownish crystals of 6.

## 3-(Pyridinyloxy)-phenylamine (8)



- 10 a) In a reaction apparatus equipped with a stirring means and a cooler, 50 g (0.53 mol) 3-hydroxypyridine, 178.8 g (1.05 mol) 1,3-dinitrobenzene and 159.9 g (1.16 mol)  $K_2CO_3$  are suspended in 1.4 l dimethyl formamide (DMF) and heated to 150 °C. After 16 hours stirring at 150 °C, the reaction mixture is cooled to room temperature and evaporated. The residue is treated with ethyl acetate (1.5 l) under stirring for 30 minutes, filtered and the filtrate is extracted with 10 % aqueous hydrochloric acid. The aqueous phase is made
- 15 alkaline with ammonium hydroxide solution and extracted with ethyl acetate. The combined organic phases are dried over  $Na_2SO_4$ , filtered and evaporated. The residue is purified by column chromatography on silica gel (1 kg) with dichloromethane as eluent, dissolved in 10 % aqueous hydrochloric acid and extracted with ethyl
- 20 acetate. The aqueous phase is made alkaline with ammonium hydroxide solution and extracted with ethyl acetate. The combined organic phases are dried over  $Na_2SO_4$ , filtered and evaporated to yield 98 g (86 %) brownish oil of 7.
- 25 b) Compound 7 is hydrogenated with Pd/C in methanol/tetrahydrofuran at room temperature. The reaction mixture is filtered over kieselguhr, the residue washed with methanol and the filtrate evaporated. The residue is digested with a diethyl ether/petroleum ether-mixture (2:1), filtered by suction, washed with petrol ether and the resulting crystals
- 30 are collected. The mother liquor is evaporated to dryness and allowed to stand in the refrigerator overnight. The resulting crystals

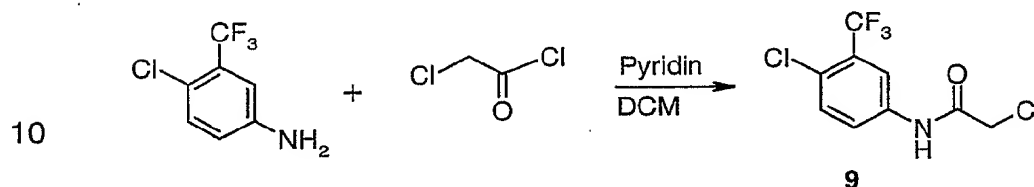


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where digested with a petroleum ether/diethyl ether-mixture (9:1) and filtered by suction. The combined crystalline residues are dried in vacuum at 40 °C overnight to yield 77.7 g (91 %) light brownish crystals of 8.

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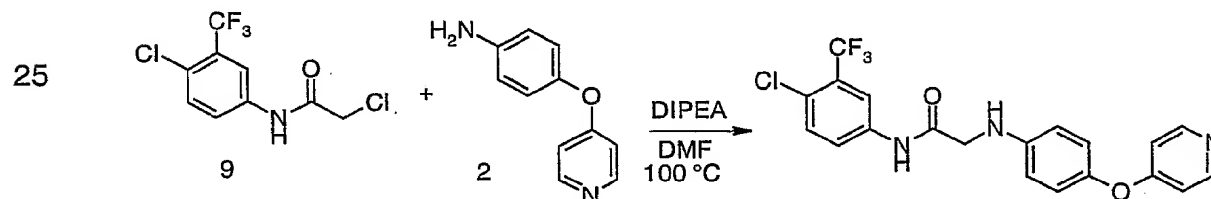
2-Chloro-N-(4-chloro-3-trifluoro methyl phenyl)-acetamide (9)



Chloroacetic acid chloride (0.69 ml; 8.44 mmol) is dropped slowly into a stirred solution of 4-chloro-3-trifluoro methyl aniline (1.5 g; 7.67 mmol) in pyridine (0.81 ml; 9.97 mmol) and dichloromethane (15 ml), cooled to 0 °C. Stirring is continued for 2 h at room temperature. The reaction mixture is diluted with dichloromethane, washed twice with 1N aqueous hydrochloric acid and with water. The reaction mixture is then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to yield 2.05 g (98 %) brownish solid of 9.

20

N-(4-Chloro-3-trifluoro methyl phenyl)-2-[4-(4-pyridinyloxy) phenyl amino]-acetamide



A solution of 146.1 mg (0.54 mmol) of compound 9 in dimethylformamide (DMF) is given to a solution of 100 mg (0.54 mmol) of compound 2 and 0.1 ml (0.59 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture

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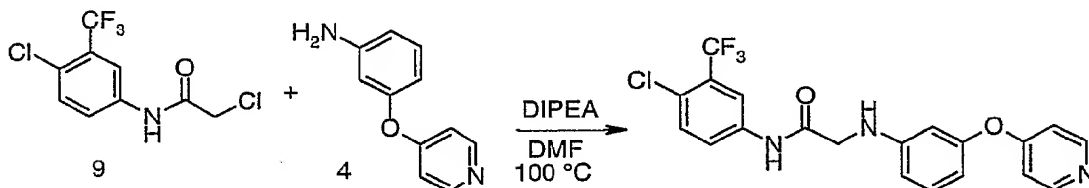
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is heated to 100 °C for 6 h, then evaporated and the residue is purified by preparative HPLC to yield 10.7 mg (5 %) colourless solid.

N-(4-Chloro-3-trifluoro methyl phenyl)-2-[3-(4-pyridinyloxy) phenyl amino]-acetamide

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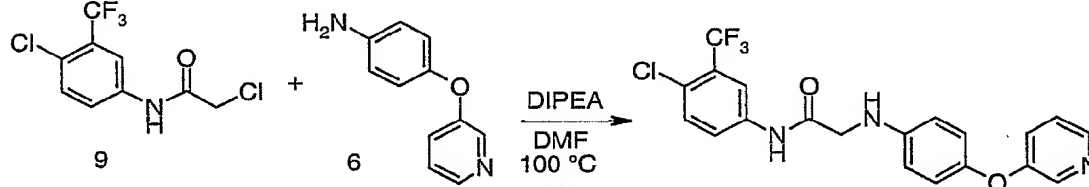


A solution of 146.1 mg (0.54 mmol) of compound 9 in dimethylformamide (DMF) is given to a solution of 100 mg (0.54 mmol) of compound 4 and 0.1 ml (0.59 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 6 h, then evaporated and the residue is purified by preparative HPLC to yield 110 mg (48 %) colourless solid.

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N-(4-Chloro-3-trifluoro methyl phenyl)-2-[4-(3-pyridinyloxy) phenyl amino]-acetamide

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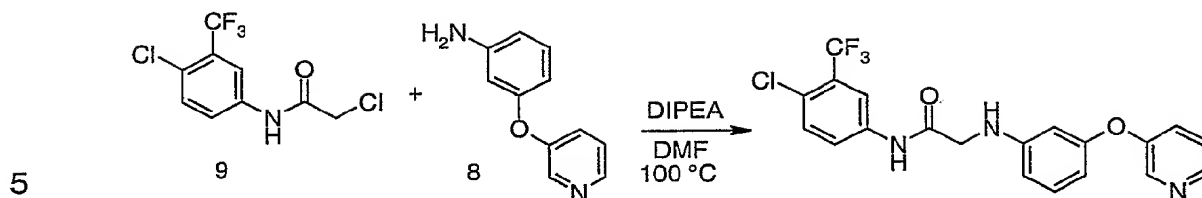
A solution of 146.1 mg (0.54 mmol) of compound 9 in dimethylformamide (DMF) is given to a solution of 100 mg (0.54 mmol) of compound 6 and 0.1 ml (0.59 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 4 h, then evaporated and the residue is purified by preparative HPLC to yield 20 mg (9 %) colourless solid.

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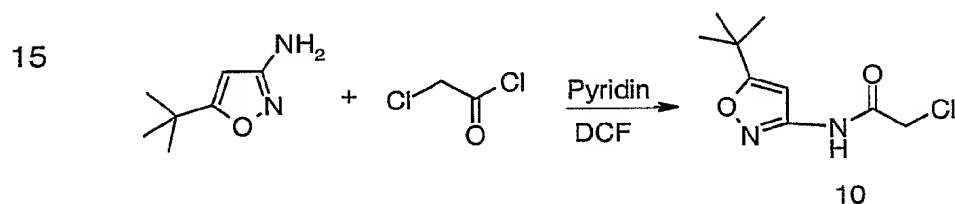
N-(4-Chloro-3-trifluoro methyl phenyl)-2-[3-(3-pyridinyloxy) phenylamine]-acetamide

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10 A solution of 146,1 mg (0.54 mmol) of compound 9 in dimethylformamide (DMF) is given to a solution of 100 mg (0.54 mmol) of compound 8 and 0.1 ml (0.59 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 4 h, then evaporated and the residue is purified by preparative HPLC to yield 24 mg (11 %) colourless solid.

#### N-(5-t-Butyl-3-isoxazolyl)-2-chloro-acetamide



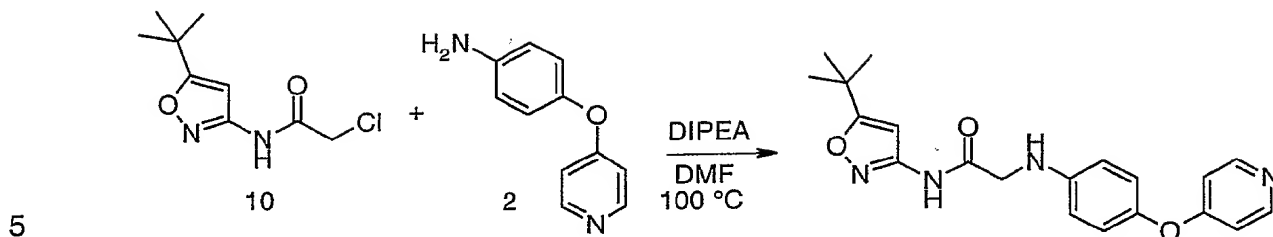
20 Chloroacetic acid chloride (0.93 ml; 11.42 mmol) is dropped slowly into a stirred solution of 5-t-Butyl-3-amino isoxazole (1.5 g; 7.67 mmol) in pyridine (1.09 ml; 13.49 mmol) and dichloromethane (20 ml), cooled to 0 °C. Stirring is continued for 2 h at room temperature. The reaction mixture is diluted with dichloromethane, washed twice with 1N aqueous hydrochloric acid, twice with an aqueous solution of NaHCO<sub>3</sub> and with water. The reaction mixture is then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to yield 2.2 g (98 %) brownish solid of 10.

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#### N-(5-t-Butyl-3-isoxazolyl)-2-[4-(4-pyridinyloxy) phenyl amino]-acetamide

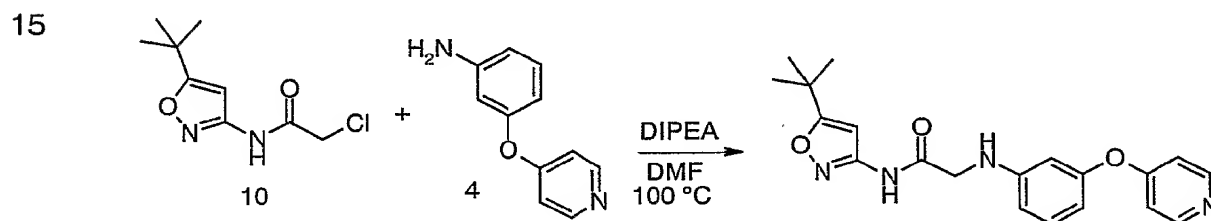
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10 A solution of 58.2 mg (0.27 mmol) of compound 10 in dimethylformamide (DMF) is given to a solution of 50 mg (0.27 mmol) of compound 2 and 0.05 ml (0.3 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 4 h, then evaporated and the residue is purified by preparative HPLC to yield 28 mg (29 %) colourless solid.

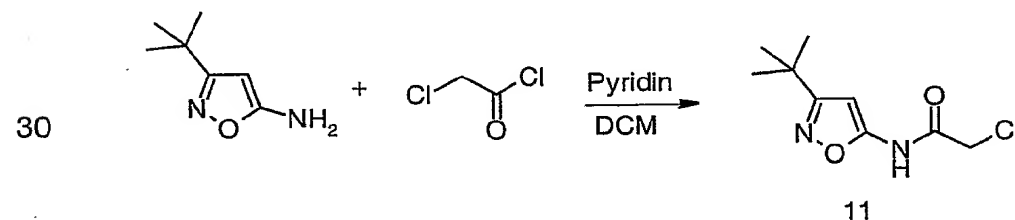
N-(5-t-Butyl-3-isoxazolyl)-2-[3-(4-pyridinyloxy) phenyl amino]-acetamide



20 A solution of 58.2 mg (0.27 mmol) of compound 10 in dimethylformamide (DMF) is given to a solution of 50 mg (0.27 mmol) of compound 4 and 0.05 ml (0.3 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 4 h, then evaporated and the residue is purified by preparative HPLC to yield 47 mg (48 %) colourless solid.

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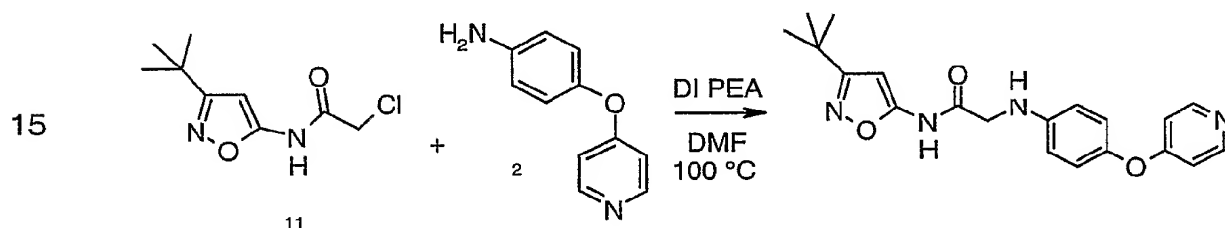
N-(3-t-Butyl-5-isoxazolyl)-2-chloro-acetamide



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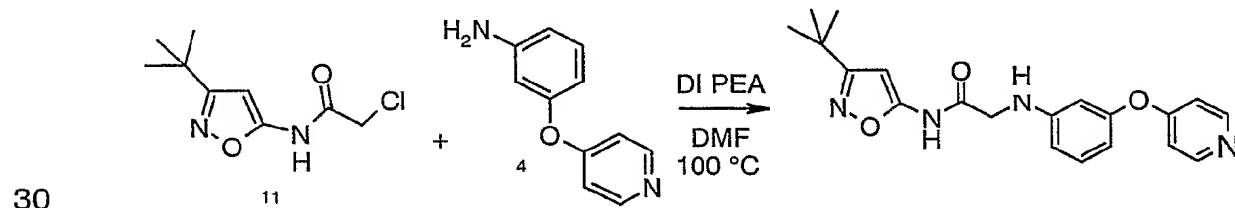
Chloroacetic acid chloride (0.25 ml; 3.14 mmol) is dropped slowly into a stirred solution of 3-t-Butyl-5-amino isoxazole (400 mg; 2.85 mmol) in pyridine (0.3 ml; 3.71 mmol) and dichloromethane (2 ml), cooled to 0 °C. Stirring is continued for 2 h at room temperature. The reaction mixture is diluted with dichloromethane, washed twice with 1N aqueous hydrochloric acid, twice with an aqueous solution of NaHCO<sub>3</sub> and with water. The reaction mixture is then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to yield 600 mg (97 %) brownish solid of 11.

N-(3-t-Butyl-5-isoxazolyl)-2-[4-(4-pyridinyloxy)phenyl amino]-acetamide



A solution of 58.2 mg (0.27 mmol) of compound 11 in dimethylformamide (DMF) is given to a solution of 50 mg (0.27 mmol) of compound 2 and 0.05 ml (0.3 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 2 h, then evaporated and the residue is purified by preparative HPLC to yield 5.5 mg (6 %) colourless solid.

N-(3-t-Butyl-5-isoxazolyl)-2-[3-(4-pyridinyloxy)phenyl amino]-acetamide



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5 A solution of 58.2 mg (0.27 mmol) of compound 11 in dimethylformamide (DMF) is given to a solution of 50 mg (0.27 mmol) of compound 4 and 0.05 ml (0.3 mmol) N-Ethyl-diisopropylamine in DMF. The reaction mixture is heated to 100 °C for 2 h, then evaporated and the residue is purified by preparative HPLC to yield 20 mg (20 %) colourless solid.

10 The compounds (1) to (235) as described above can preferably be produced according to the procedures described herein or in an analogous manner thereof.

#### **Example A: Injection vials**

15 A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2N hydrochloric acid, sterile-filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

#### **Example B: Suppositories**

20 A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

#### **Example C: Solution**

25 A solution of 1 g of an active compound of the formula I, 9.38 g of  $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$ , 28.48 g of  $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$  and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water is prepared. It is adjusted to pH  
30 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

**Example D: Ointment**

5 500 mg of an active compound of the formula I is mixed with 99.5 g of petroleum jelly under aseptic conditions.

**Example E: Tablets**

10 A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to give tablets in a customary manner such that each tablet contains 10 mg of active compound.

**Example F: Coated tablets**

15 Analogously to Example E, tablets are pressed and are then coated in a customary manner using a coating of sucrose, potato starch, talc, tragacanth and colourant.

**Example G: Capsules**

20 2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

25

**Example H: Ampoules**

30 A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

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**Claims**

## 1. Glycinamide derivatives of formula I

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A-D-B

(I)

wherein

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D is a bivalent glycine amide moiety, or a derivative thereof,

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A is a unsubstituted or substituted moiety of up to 40 carbon atoms of the formula:  $-L-(M-L')_{\alpha}$ , where L is a 5, 6 or 7 membered cyclic structure, preferably selected from the group consisting of aryl, heteroaryl, arylene and heteroarylene, bound directly to D, L' comprises an optionally substituted cyclic moiety having at least 5 members, preferably selected from the group consisting of aryl, heteroaryl, aralkyl, cycloalkyl and heterocyclyl, M is a bond or a bridging group having at least one atom,  $\alpha$  is an integer of from 1-4; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein L' is preferably substituted by at least one substituent selected from the group consisting of  $-SO_2R_x$ ,  $-C(O)R_x$  and  $-C(NR_y)R_z$ ,

20

25

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms, preferably of up to 20 carbon atoms, comprising at least one 5-, 6-, or 7-membered cyclic structure, preferably a 5- or 6-membered cyclic structure, bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein said cyclic structure directly bound to D is preferably selected from the group

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consisting of aryl, heteroaryl and heterocyclyl,  $R_y$  is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

5

$R_z$  is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

10

$R_x$  is  $R_z$  or  $NR_aR_b$ , where  $R_a$  and  $R_b$  are

15

a) independently hydrogen, a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

20

$-OSi(R_f)_3$  where  $R_f$  is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

25

30

or

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- 5 b)  $R_a$  and  $R_b$  together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or
- 10 c) one of  $R_a$  or  $R_b$  is  $-C(O)-$ , a  $C_1-C_5$  divalent alkylene group or a substituted  $C_1-C_5$  divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted  $C_1-C_5$  divalent alkylene group are selected from the group consisting of
- 15 halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;
- 20 where B is substituted, L is substituted or L' is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and  $W^\gamma$ , where  $\gamma$  is 0-3;
- 25 wherein each W is independently selected from the group consisting of  $-CN$ ,  $-CO_2R$ ,  $-C(O)NR^5R^5$ ,  $-C(O)-R^5$ ,  $-NO_2$ ,  $-OR^5$ ,  $-SR^5$ ,  $-SO_2R^5$ ,  $-SO_3H$ ,  $-NR^5R^5$ ,  $-NR^5C(O)OR^5$ ,  $-NR^5C(O)R^5$ ,  $-Q-Ar$ , and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the groups
- 30 consisting of  $-CN$ ,  $-CO_2R$ ,  $-C(O)NR^5R^5$ ,  $-C(O)-R^5$ ,  $-NO_2$ ,  $-OR^5$ ,  $-SR^5$ ,  $-SO_2R^5$ ,  $-SO_3H$ ,  $-NR^5R^5$ ,  $-NR^5C(O)OR^5$ , -

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- $\text{NR}^5\text{C}(\text{O})\text{R}^5$  and halogen up to per-halo; with each  $\text{R}^5$  independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, wherein Q is -O-, -S-, -N( $\text{R}^5$ )-, -( $\text{CH}_2$ ) $\beta$ -, -C(O)-, -CH(OH)-, -( $\text{CH}_2$ ) $\beta$ O-, -( $\text{CH}_2$ ) $\beta$ S-, -( $\text{CH}_2$ ) $\beta$ N( $\text{R}^5$ )-, -O( $\text{CH}_2$ ) $\beta$ -, -CHHal-, -CHal $_2$ -, -S-( $\text{CH}_2$ )- and -N( $\text{R}^5$ )( $\text{CH}_2$ ) $\beta$ - where  $\beta = 1-3$ , and Hal is halogen; and Ar is 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by  $\text{Z}_{\delta 1}$  wherein  $\delta 1$  is 0 to 3 and each Z is independently selected from the group consisting -CN, -CO $_2\text{R}^5$ , -C(O)NR $^5\text{R}^5$ , -C(O)-R $^5$ , -NO $_2$ , -OR $^5$ , -SR $^5$ , -SO $_2\text{R}^5$ , -SO $_3\text{H}$ , -NR $^5\text{R}^5$ , -NR $^5\text{C}(\text{O})\text{OR}^5$ , -NR $^5\text{C}(\text{O})\text{R}^5$ , and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO $_2\text{R}^5$ , -C(O)NR $^5\text{R}^5$ , -C(O)-R $^5$ , -NO $_2$ , -OR $^5$ , -SR $^5$ , -SO $_2\text{R}^5$ , -SO $_3\text{H}$ , -NR $^5\text{R}^5$ , -NR $^5\text{C}(\text{O})\text{OR}^5$ , -NR $^5\text{C}(\text{O})\text{R}^5$ , and the the physiologically acceptable derivatives, salts and solvates thereof.
2. Glycinamide derivative according to claim 1, characterised in that each M independently from one another represents a bond or is a bridging group, selected from the group consisting of (CR $^5\text{R}^5$ ) $_h$ , or (CHR $^5$ ) $_h$ -Q-(CHR $^5$ ) $_i$ , wherein
- Q is selected from a group consisting of O, S, N-R $^5$ , (CHal $_2$ ) $_j$ , (O-CHR $^5$ ) $_j$ , (CHR $^5$ -O) $_j$ , CR $^5$ =CR $^5$ , (O-CHR $^5$ CHR $^5$ ) $_j$ ,

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$(\text{CHR}^5\text{CHR}^5\text{-O})_j$ ,  $\text{C=O}$ ,  $\text{C=S}$ ,  $\text{C=NR}^5$ ,  $\text{CH(OR}^5\text{)}$ ,  $\text{C(OR}^5\text{)(OR}^5\text{)}$ ,  
 $\text{C(=O)O}$ ,  $\text{OC(=O)}$ ,  $\text{OC(=O)O}$ ,  $\text{(C=O)N(R}^5\text{)C(=O)}$ ,  $\text{OC(=O)N(R}^5\text{)}$ ,  
 $\text{N(R}^5\text{)C(=O)O}$ ,  $\text{CH=N-NR}^5$ ,  $\text{S=O}$ ,  $\text{SO}_2$ ,  $\text{SO}_2\text{NR}^5$  und  $\text{NR}^5\text{SO}_2$ ,  
 wherein

5

$\text{R}^5$  is in each case independently selected from the meanings given  
 above, preferably hydrogen, halogen, alkyl, aryl, aralkyl,

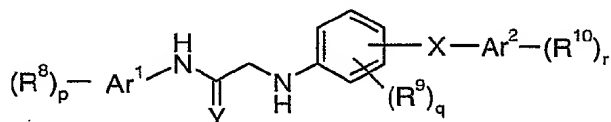
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$h, i$  are independently from each other 0, 1, 2, 3, 4, 5, or 6,  
 preferably 0, 1, 2 or 3, and

$j$  is 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3.

15

3. Glycinamide derivative according to claim 1 or 2, selected from the  
 compounds of formula II,



II

20

wherein

25

$\text{Ar}^1, \text{Ar}^2$  are selected independently from one another from  
 aromatic hydrocarbons containing 6 to 14 carbon atoms  
 and ethylenical unsaturated or aromatic heterocyclic  
 residues containing 3 to 10 carbon atoms and one or two  
 hetero atoms, independently selected from N, O und S,

30

$\text{R}^8, \text{R}^9$   
 and  $\text{R}^{10}$  are independently selected from a group  
 consisting of H, A, cycloalkyl comprising 3 to 7 carbon  
 atoms, Hal,  $\text{CH}_2\text{Hal}$ ,  $\text{CH(Hal)}_2$ ,  $\text{C(Hal)}_3$ ,  $\text{NO}_2$ ,  $(\text{CH}_2)_n\text{CN}$ ,

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$(CH_2)_nNR^{11}R^{12}$ ,  $(CH_2)_nOR^{11}$ ,  $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$ ,  
 $(CH_2)_nCOOR^{12}$ ,  $(CH_2)_nCONR^{11}R^{12}$ ,  $(CH_2)_nNR^{11}COR^{13}$ ,  
 $(CH_2)_nNR^{11}CONR^{11}R^{12}$ ,  $(CH_2)_nNR^{11}SO_2A$ ,  
 $(CH_2)_nSO_2NR^{11}R^{12}$ ,  $(CH_2)_nS(O)_uR^{13}$ ,  $(CH_2)_nOC(O)R^{13}$ ,  
 $(CH_2)_nCOR^{13}$ ,  $(CH_2)_nSR^{11}$ ,  $CH=N-OA$ ,  $CH_2CH=N-OA$ ,  
 $(CH_2)_nNHOA$ ,  $(CH_2)_nCH=N-R^{11}$ ,  $(CH_2)_nOC(O)NR^{11}R^{12}$ ,  
 $(CH_2)_nNR^{11}COOR^{12}$ ,  $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$ ,  
 $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$ ,  $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$ ,  
 $C(R^{13})HCOOR^{12}$ ,  $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{12}$ ,  
 $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$ ,  $CH=CHCOOR^{11}$ ,  
 $CH=CHCH_2NR^{11}R^{12}$ ,  $CH=CHCH_2NR^{11}R^{12}$ ,  
 $CH=CHCH_2OR^{13}$ ,  $(CH_2)_nN(COOR^{11})COOR^{12}$ ,  
 $(CH_2)_nN(CONH_2)COOR^{11}$ ,  $(CH_2)_nN(CONH_2)CONH_2$ ,  
 $(CH_2)_nN(CH_2COOR^{11})COOR^{12}$ ,  
 $(CH_2)_nN(CH_2CONH_2)COOR^{11}$ ,  
 $(CH_2)_nN(CH_2CONH_2)CONH_2$ ,  $(CH_2)_nCHR^{13}COR^{11}$ ,  
 $(CH_2)_nCHR^{13}COOR^{11}$ ,  $(CH_2)_nCHR^{13}CH_2OR^{14}$ ,  $(CH_2)_nOCN$   
 and  $(CH_2)_nNCO$ , wherein

$R^{11}$ ,  $R^{12}$  are independently selected from a group consisting of H,  
 A,  $(CH_2)_mAr^3$  and  $(CH_2)_mHet$ , or in  $NR^{11}R^{12}$ ,

$R^{11}$  and  $R^{12}$  form, together with the N-Atom they are bound to,  
 a 5-, 6- or 7-membered heterocyclis which optionally  
 contains 1 or 2 additional hetero atoms, selected from  
 N, O an S,

$R^{13}$ ,  $R^{14}$  are independently selected from a group consisting of H,  
 Hal, A,  $(CH_2)_mAr^4$  and  $(CH_2)_mHet$ ,

A is selected from the group consisting of alkyl, alkenyl,  
 cycloalkyl, alkylencycloalkyl, alkoxy and alkoxyalkyl,

- 5  $Ar^3, Ar^4$  are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal,  $NO_2$ , CN,  $OR^{15}$ ,  $NR^{15}R^{16}$ ,  $COOR^{15}$ ,  $CONR^{15}R^{16}$ ,  $NR^{15}COR^{16}$ ,  $NR^{15}CONR^{15}R^{16}$ ,  $NR^{16}SO_2A$ ,  $COR^{15}$ ,  $SO_2R^{15}R^{16}$ ,  $S(O)_uA$  and  $OOCR^{15}$ ,
- 10 Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal,  $NO_2$ , CN,  $OR^{15}$ ,  $NR^{15}R^{16}$ ,  $COOR^{15}$ ,  $CONR^{15}R^{16}$ ,  $NR^{15}COR^{16}$ ,  $NR^{15}CONR^{15}R^{16}$ ,  $NR^{16}SO_2A$ ,  $COR^{15}$ ,  $SO_2R^{15}R^{16}$ ,  $S(O)_uA$  and  $OOCR^{15}$ ,
- 15  $R^{15}, R^{16}$  are independently selected from a group consisting of H, A, and  $(CH_2)_mAr^5$ , wherein
- 20  $Ar^6$  is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH,  $NH_2$  and  $CF_3$ ,
- 25 n, m are independently of one another 0, 1, 2, 3, 4, or 5;
- X represents a bond or is  $(CR^{11}R^{12})_h$ , or  $(CHR^{11})_h-Q-(CHR^{12})_i$ , wherein
- 30 Q is selected from a group consisting of O, S,  $N-R^{15}$ ,  $(CHal_2)_j$ ,  $(O-CHR^{18})_j$ ,  $(CHR^{18}-O)_j$ ,  $CR^{18}=CR^{19}$ ,  $(O-CHR^{18}CHR^{19})_j$ ,  $CHR^{18}CHR^{19}-O)_j$ , C=O, C=S, C=NR<sup>15</sup>, CH(OR<sup>15</sup>),

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$C(OR^{17})(OR^{20})$ ,  $C(=O)O$ ,  $OC(=O)$ ,  $OC(=O)O$ ,  $C(=)N(R^{15})$ ,  
 $N(R^{15})C(=O)$ ,  $OC(=O)N(R^{15})$ ,  $N(R^{15})C(=O)O$ ,  $CH=N-O$ ,  
 $CH=N-NR^{15}$ ,  $OC(O)NR^{15}$ ,  $NR^{15}C(O)O$ ,  $S=O$ ,  $SO_2$ ,  $SO_2NR^{15}$   
und  $NR^{15}SO_2$ , wherein

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$h, i$  are independently from each other 0, 1, 2, 3, 4, 5 or 6, and

$j$  is 1, 2, 3, 4, 5 or 6,

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$Y$  is selected from  $O$ ,  $S$ ,  $NR^{21}$ ,  $C(R^{22})-NO_2$ ,  $C(R^{22})-CN$  and  $C(CN)_2$ , wherein

$R^{21}$  is independently selected from the meanings given for  $R^{13}$ ,  $R^{14}$ , and

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$R^{22}$  is independently selected from the meanings given for  $R^{11}$ ,  $R^{12}$ ,

$p, r$  are independently from one another 0, 1, 2, 3, 4 or 5,

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$q$  is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

$u$  is 0, 1, 2 or 3, preferably 0, 1 or 2,

25

and

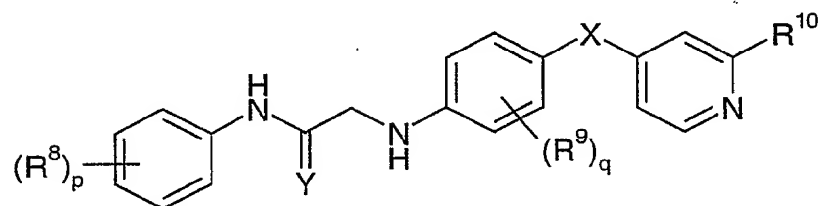
$Hal$  is independently selected from a group consisting of  $F$ ,  $Cl$ ,  $Br$  and  $I$ ;

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and the salts and solvates thereof.

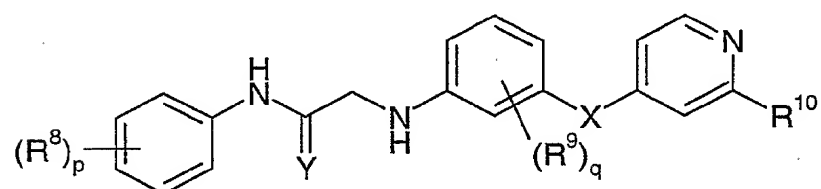
4. Glycinamide derivative according to one of the claims 1 to 3, selected from the compounds of formula IIa, IIb, IIc, IId, IIe, IIg and IIh,

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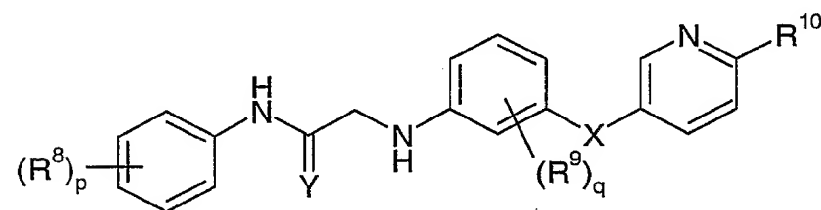
IIa

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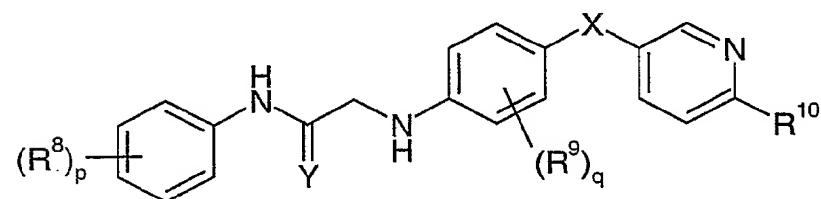
IIb

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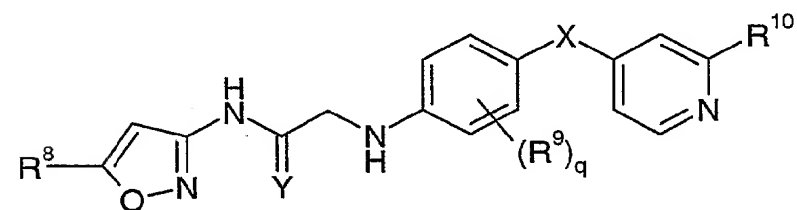
IIc

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IId

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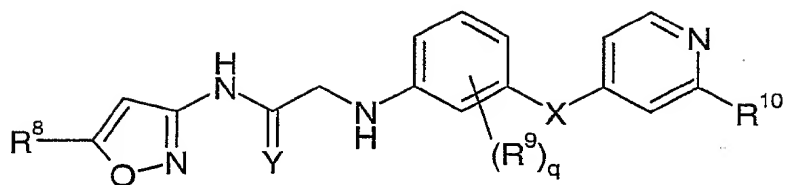


IIe

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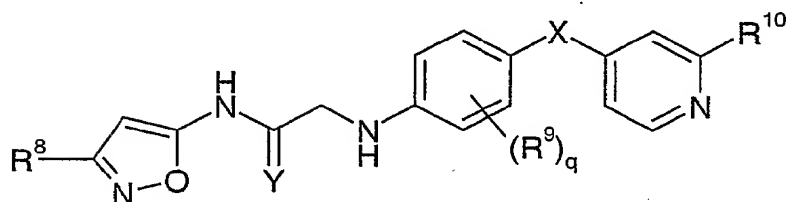


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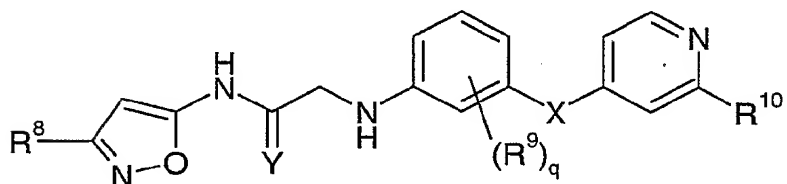
II f

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II g

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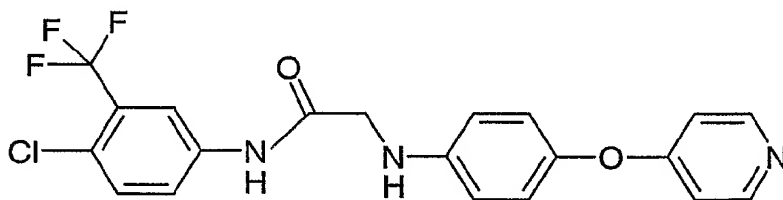
II h

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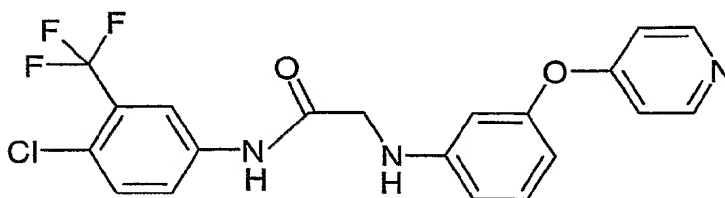
wherein  $R^8$ ,  $p$ ,  $Y$ ,  $R^9$  and  $q$  are as defined in claim 3, and  $R^{10}$  is H or as defined in claim 3; and the salts and solvates thereof.

5. Glycinamide derivative according to claim 1 or 2, selected from

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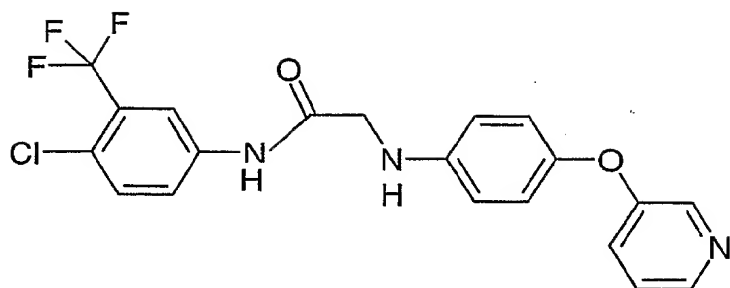
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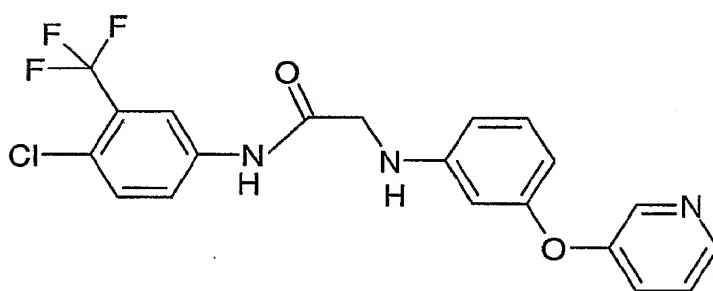
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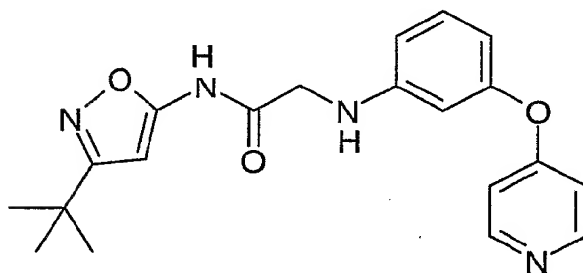


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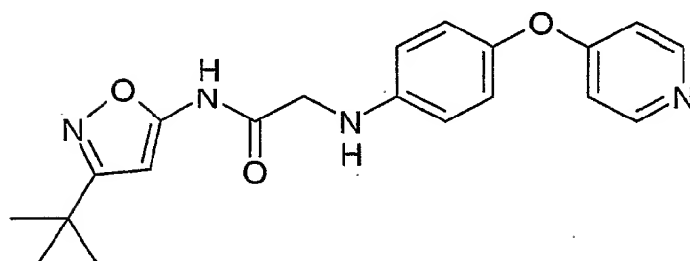


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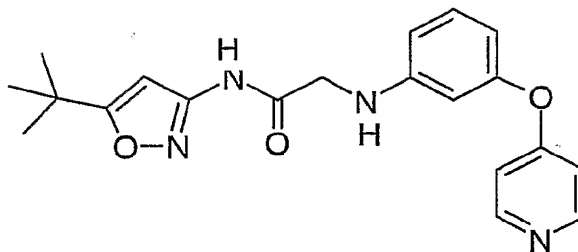
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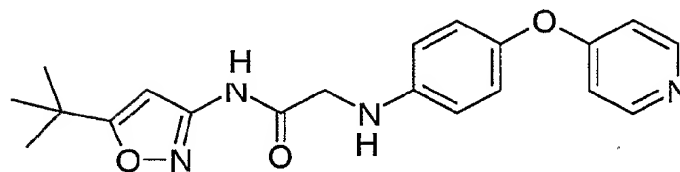
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6. Glycinamide derivative according to one of the claims 1 to 5 as a medicament.

7. Glycinamide derivative according to one of the claims 1 to 5 as a kinase inhibitor.

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8. Glycinamide derivative according to claim 7, characterized in that the kinases are selected from raf-kinases.

9. Pharmaceutical composition, characterized in that it contains one or more compounds according to one of the claims 1 to 5.

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10. Pharmaceutical composition according to claim 9, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5.

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11. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the

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- 5       claims 1 to 5 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5, is processed by mechanical means into a pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.
- 10       12. Use of a compound according to one of the claims 1 to 5 as a pharmaceutical.
13. Use of a compound according to one of the claims 1 to 5 in the treatment and/or prophylaxis of disorders.
- 15       14. Use of a compound according to one of the claims 1 to 5 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.
- 20       15. Use according to claim 13 or 14, characterised in that the disorders are caused, mediated and/or propagated by raf-kinases.
16. Use according to claim 13, 14 or 15, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.
- 25       17. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is cancer.
18. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is noncancerous.
- 30       19. Use according to claim 13, 14, 15, 16 or 18, characterised in that the noncancerous disorders are selected from the group consisting of

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infection, psoriasis, arthritis, inflammation, endometriosis, scarring, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.

- 5        20. Use according to one of the claims 13 to 17, characterised in that the disorders are selected from the group consisting of brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, 10 gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.
- 15        21. Use according to one of the claims 13 to 16, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation and neurodegenerative diseases. 20
22. Use of a compound according to one of the claims 1 to 5 as a raf-kinase inhibitor.
- 25        23. Use according to claim 22, characterised in that the raf-kinase is selected from the group consisting of A-Raf, B-Raf and c-Raf-1.
- 30        24. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 5 is administered to a patient in need of such a treatment.
25. Method according to claim 24, characterised in that the one or more compounds according to one of the claims claim 1 to 5 are

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administered as a pharmaceutical composition according to claim 9 or 10.

26. Method for the treatment and/or prophylaxis of disorders according to claim 25, characterised in that the disorders are as defined in one of the claims 15 to 21.

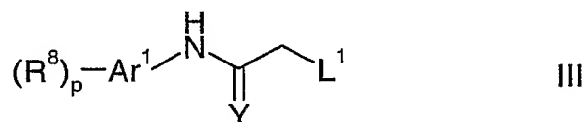
27. Method for the treatment according to claim 26, characterised in that the disorders is cancerous cell growth mediated by raf-kinase.

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28. Method for producing compounds of formula II, characterised in that

a) a compound of formula III

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wherein

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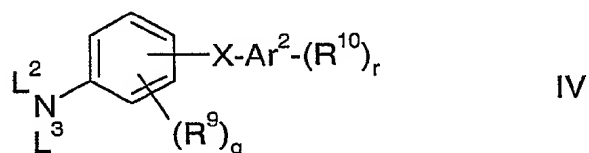
$L^1$  is Cl, Br, I, OH, a reactive esterified OH-group or a diazonium moiety, and  $R^8$ ,  $p$ ,  $Ar^1$ ,  $Y$  are as defined in claim 3,

is reacted

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b) with a compound of formula IV,

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wherein

$L^2$ ,  $L^3$  are independently from one another H or a metal ion, and  $R^9$ ,  
q, X,  $Ar^2$ ,  $R^{10}$  and r are as defined in claim 3,

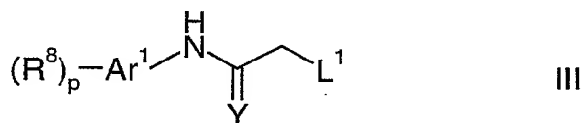
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and optionally

isolating and/or treating the compound of formula II obtained by said  
reaction with an acid, to obtain the salt thereof.

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29. Compound of formula III,



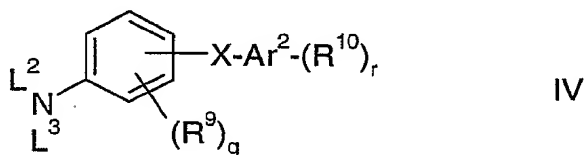
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wherein

$L^1$  is Cl, Br, I, OH, a reactive esterified OH-group or a diazonium  
moiety, and  $R^8$ , p,  $Ar^1$ , Y are as defined in claim 3.

20

30. Compound of formula IV,



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wherein

$L^2$ ,  $L^3$  are independently from one another H or a metal ion, and  $R^9$ , q, X,  
 $Ar^2$ ,  $R^{10}$  and r are as defined in claim 3.

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# INTERNATIONAL SEARCH REPORT

Internatio	Application No
PCT/EP 03/08474	

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4409 A61K31/4427 C07D213/68 C07D413/12 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 26197 A (SQUIBB BRISTOL MYERS CO) 11 May 2000 (2000-05-11) see claim 1 and examples 1-3 on pages 45-49 ---	3
X	WO 94 20467 A (BOEHRINGER MANNHEIM GMBH ; SAAL WOLFGANG VON DER (DE); HECK REINHAR) 15 September 1994 (1994-09-15) see claim 12, formula II and examples ---	3
X	EP 0 519 353 A (FUJISAWA PHARMACEUTICAL CO) 23 December 1992 (1992-12-23) see claim 1 and examples ---	3
X	US 5 741 926 A (BIERER DONALD E ET AL) 21 April 1998 (1998-04-21) see formula I, column 9 and examples --- -/--	3

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

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Date of the actual completion of the international search

6 November 2003

Date of mailing of the international search report

13/11/2003

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## INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAKEUCHI ET AL.: "Synthesis and antitumor activity of fused quinoline derivatives" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 40, no. 6, 1992, pages 1481-1485, XP001079692 see compound 7 -----	3
X	SHAH ET AL.: "Studies on Acetamide derivatives" J. INDIAN CHEM. SOC., vol. 64, no. 11, 1987, pages 678-681, XP009020095 see compounds (4) -----	3
X	COLOMBO ET AL.: "Pharmacological study of a series of aminoacetanilides with local anesthetic activity" REVISTA DE FARMACOLOGIA CLINICA Y EXPERIMENTAL, vol. 4, no. 1, 1987, pages 41-47, XP009020107 see table on page 44, compound E-3305 -----	3
X	SCHANKER ET AL.: "Synthesis and Biological Activities of sulphanilamides" CURRENT SCIENCE, vol. 53, no. 20, 1984, pages 1069-1071, XP009020091 see table 1 -----	3

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/EP 03/08474

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0026197	A	11-05-2000	AU 1707700 A	22-05-2000
			CA 2348267 A1	11-05-2000
			EP 1127054 A1	29-08-2001
			JP 2002528533 T	03-09-2002
			WO 0026197 A1	11-05-2000
			US 6624184 B1	23-09-2003
WO 9420467	A	15-09-1994	DE 4306506 A1	08-09-1994
			DE 4312966 A1	27-10-1994
			AT 174590 T	15-01-1999
			AU 682026 B2	18-09-1997
			AU 6257494 A	26-09-1994
			CA 2156729 A1	15-09-1994
			CN 1119858 A ,B	03-04-1996
			CZ 9502254 A3	17-01-1996
			DE 59407494 D1	28-01-1999
			DK 687253 T3	23-08-1999
			WO 9420467 A1	15-09-1994
			EP 0687253 A1	20-12-1995
			ES 2127919 T3	01-05-1999
			FI 954105 A	01-09-1995
			GR 3029691 T3	30-06-1999
			HU 72898 A2	28-06-1996
			IL 108786 A	11-04-1999
			JP 8507503 T	13-08-1996
			KR 252551 B1	01-05-2000
			NO 953447 A	01-09-1995
			NZ 262725 A	26-05-1997
			PL 310520 A1	27-12-1995
			RU 2126388 C1	20-02-1999
			SK 108295 A3	05-06-1996
			ZA 9401445 A	04-09-1995
EP 0519353	A	23-12-1992	AT 195521 T	15-09-2000
			AU 656197 B2	27-01-1995
			AU 1827092 A	24-12-1992
			CA 2071375 A1	18-12-1992
			CN 1067893 A ,B	13-01-1993
			DE 69231350 D1	21-09-2000
			DE 69231350 T2	04-01-2001
			DK 519353 T3	18-09-2000
			EP 0519353 A2	23-12-1992
			ES 2149160 T3	01-11-2000
			GR 3034429 T3	29-12-2000
			HU 61544 A2	28-01-1993
			HU 9500394 A3	28-09-1995
			IE 921805 A1	30-12-1992
			JP 2663794 B2	15-10-1997
			JP 5178856 A	20-07-1993
			KR 244879 B1	02-03-2000
			MX 9202901 A1	01-05-1993
			PT 519353 T	29-12-2000
			RU 2120942 C1	27-10-1998
			US 5334716 A	02-08-1994
			ZA 9203958 A	24-02-1993
US 5741926	A	21-04-1998	NONE	